The New England
Journal of Medicine

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VOLUME 226 JANUARY 22, 1942 NUMBER 4

SALMONELLA SUIPESTIFER INFECTION IN BOSTON*

A Report of Eleven Cases, with Autopsy Findings in a Case of Bacterial Endocarditis Due to this Organism, and a Study of the Agglutination Reactions in this Infection

N. ERNEST GOULDER, M.D.,† MARGARET F. KINGSLAND, A.B.,‡ AND CHARLES A. JANEWAY, M.D.§

BOSTON

ALTHOUGH *Salmonella suipestifer*¶ infection has been infrequently reported in New England, it has occurred often enough in our experience to warrant emphasis on some of its peculiarities. The organism now known as *S. suipestifer* was isolated in 1885 by Salmon and Smith from swine with hog cholera. This disease of swine is now known to be caused by a filterable virus, but it is frequently complicated by an acute intestinal inflammation due to *S. suipestifer*. In 1902, Longcope[1] reported 2 cases of infection in man caused by an organism that was later identified by TenBroeck as belonging to the *suipestifer* group.

During World War I, suipestifer organisms were identified as the causative agents of a number of mild epidemics of acute gastroenteritis. In 1919, MacAdam[2] reported an epidemic in Mesopotamia, and Hirschfeld reported one in Serbia. Since then, many reports of similar epidemics have been published, and by 1937 Harvey[3] had compiled a total of 1425 cases occurring in epidemics. From these studies, it became evident that the epidemic form of infection was characterized by a brief incubation period, followed by the abrupt onset of fever, headache, abdominal pain, vomiting and diarrhea, fairly rapid recovery and a very low mortality. This organism must therefore be considered a possible etiologic agent in an epidemic of so-called "food poisoning."

*From the Pathology Laboratory and the Medical Clinic, Peter Bent Brigham Hospital; the Boston Lying-in Hospital; and the Department of Pathology, Department of Medicine and Department of Bacteriology and Immunology, Harvard Medical School.

†Graduate assistant in pathology, Peter Bent Brigham Hospital.

‡Bacteriologist, Peter Bent Brigham Hospital.

§Associate in medicine, Peter Bent Brigham Hospital; instructor in medicine and in bacteriology and immunology, Harvard Medical School; consulting bacteriologist, Boston Lying-in Hospital.

¶Although the official name for *Salmonella suipestifer* is *S. cholerae suis*, the former name is so much more familiar that we have continued to use it in the text. For the nomenclature and classification of the commoner members of the Salmonella group, see Table 3.

Once the epidemic form of the infection became known, sporadic cases began to be reported, characterized by diverse clinical findings and by a very high mortality rate in adults. In his 1937 review, Harvey[3] listed approximately 70 cases of this type. Bacteremia has been noted in about 60 per cent of these sporadic cases. Clinically, the patients are often without localizing signs of infection and present a typhoidal picture characterized by an acute onset, marked fever lasting from two to ten days, headache, anorexia, vomiting, coryza, dry cough and abdominal pain. In a few cases, shaking chills, joint pains or diarrhea may occur, and children may show drowsiness, meningismus and even convulsions. As in typhoid fever, the white-cell count tends to be depressed unless the infection localizes. Although the organism is readily cultured from the blood, it is rarely observed in the stools.

When localization of the infection occurs, the lungs appear to be a site of predilection, for bronchopneumonia develops in about 30 per cent of the patients. The clinical course is characterized by high fever, daily variations in temperature as great as 2°F. and a gradual subsidence. Rarely is the organism found in the sputum; Bullowa,[4] in 1928, reported one such case, which was associated with lobar pneumonia. Pleural effusion, a rare finding, was reported by Boller[3] in 1930, by Cohen, Fink and Gray[5] in 1936, and by Harvey[3] in 1937.

Other frequent sites of localization are the bones and joints. Pyarthrosis and osteomyelitis appear in 20 per cent of the cases several days to a few weeks after the onset of the infection. The involved joint is warm, swollen and tender and, on aspiration, yields greenish fluid from which the organism may be cultured. Osteomyelitis of ad

joining bones frequently develops, and with the progression of the disease, the usual x-ray findings appear.

Purulent meningitis characterized by coma, convulsions, cervical rigidity and a positive Kernig sign was reported by Materna and Januschke[3] in 1925, by Kuttner and Zepp[6] in 1932, by Boycott and McNee[7] in 1936, and by Ravitch and Washington[8] in 1937. A case of pericarditis was described in 1936 by Cohen, Fink and Gray.[5] Clifton and Werner,[9] in 1938, presented a patient with bilateral subdural abscesses. Although the urinary tract is usually spared in these infections, mild cystitis has occasionally occurred. Other urinary-tract complications are rare, but in 1918, Neukirch[10] reported a case of pyelonephritis, and in 1925, Ssokoloff[3] described a case of perinephric abscess.

From this survey of the clinical features of suipestifer infections, it is apparent that although the disease tends to follow a typhoidal course, it may localize in any one of a number of sites, of which the lungs, bones and joints are the commonest. Furthermore, the infection appears oftenest under conditions that reduce the resistance of the patient. Suipestifer epidemics therefore tend to develop in populations already weakened by starvation and exposure, and sporadic cases often appear in people suffering from some chronic disease, such as diabetes, malaria, tuberculosis or neoplasm.* This fact may account for the typical high mortality rate.

Suipestifer Bacterial Endocarditis

The occurrence of bacterial endocarditis in suipestifer infections has been mentioned only in recent years. In 1931, TenBroeck, Li and Yü[12] reported a case of acute vegetative mitral endocarditis in a patient with blood cultures positive for *Bacterium paratyphosum* C, which belongs to the suipestifer group. Gouley and Israel,[13] in 1934, studied a case of suipestifer bacteremia in a four-year-old boy who developed a rough mitral murmur and later a double aortic murmur during his illness. Inasmuch as the child recovered, the clinical diagnosis of suipestifer endocarditis could not be proved. In 1939, Forster[14] reported 2 cases of fatal bacterial endocarditis that were proved to be due to *S. suipestifer* by bacteriologic studies at necropsy. One patient was a forty-seven-year-old Negro with tertiary syphilis who developed fever, leukocytosis and an apical systolic murmur of increasing intensity. Three blood cultures were positive for *S. suipestifer* (American type). At post-mortem examination, the heart showed syphilitic aortitis, with extension to the myocardium, and acute ulcerative mural endocarditis of the right atrium and left ventricle. The second was a thirty-one-year-old laborer with rheumatic heart disease, who developed a spiking temperature, chills, leukocytosis and a variable diastolic murmur; seven blood cultures were positive for *S. suipestifer* (American type). At post-mortem examination, the heart showed chronic rheumatic pancarditis, with focal epicarditis, fibrosis of the aortic, mitral and tricuspid valves, and acute ulcerative mitral endocarditis. In both cases, the bacillus was recovered from the endocardial vegetations; the hearts had already been damaged by chronic disease, and the clinical course in each was stormy, with fever, leukocytosis and rapid progression. Later in 1939, Read[15] reported a third case of *S. suipestifer* endocarditis proved at autopsy. This occurred in a forty-nine-year-old woman with a rapidly enlarging abdominal tumor, considered to be an ovarian cyst. On paracentesis, the fluid removed from the cyst was found to contain *S. suipestifer* (European type). Septicemia due to this organism developed after operation, and systolic and diastolic murmurs appeared at the aortic area. At post-mortem examination, the heart showed acute bacterial aortic valvulitis, but there was no evidence of antecedent injury. We report below a fourth case of *S. suipestifer* endocarditis, which was studied in 1940 on the medical wards of the Peter Bent Brigham Hospital.

Case Report

Case 1. S. W. (P. B. B. H. 57907), a 58-year-old Russian-born housewife, entered the hospital on September 6, 1940, because of chills and fever of 3 days' duration. She had had an attack of "rheumatism" at the age of 26, and a heart murmur had been noted at the age of 32. For many years, she had experienced gaseous indigestion and heartburn after eating fried foods. For 4 years, she had noticed increasing shortness of breath on exertion. Three days before entry, she had a severe chill, followed by headache and fever, and accompanied by vomiting and knifelike epigastric pain. These symptoms persisted, and hospitalization was advised. One month before this episode, she had spent 2 weeks in the country, where she drank raw milk and well water, but no one else in her party had become ill.

Physical examination revealed an elderly obese woman, drowsy, mildly confused and dehydrated, who had a temperature of 103°F., a pulse of 95, respirations of 30 and a blood pressure of 120/70. The conjunctivas were injected, the pupils and fundi were normal, and the tongue was heavily coated. The heart was moderately enlarged to the left, with a prominent systolic thrill in the aortic area, and also at the apex. A loud, rough systolic murmur

*One of the most striking examples of the course of suipestifer infection in a patient with neoplasm was reported by Gray[11] in 1936. The patient, a 36-year-old Negress with a suipestifer bacteremia, ran a prolonged febrile course due to abscesses in myomas of the uterus. These presumably acted as foci for reinfection. After a supravaginal hysterectomy, the patient recovered.

was heard in both areas. The pulse at the wrist was of the plateau type. Although there was slight epigastric tenderness, neither the spleen nor the liver was palpable.

The blood Hinton and Wassermann reactions were negative. The urine showed small amounts of protein at times, an occasional red blood cell and 3 to 4 white blood cells per high-power field, and occasional hyaline and granular casts in the centrifuged sediment. The red-cell count fell progressively from 4,550,000 to 2,700,000, and the hemoglobin from 93 per cent to 60 per cent (Sahli). The white-cell count decreased from 21,000 to 13,000, and 90 per cent of the white blood cells in stained blood smears were neutrophils. The sedimentation rate was 44 mm. per hour (Wintrobe). Blood chemical findings included chlorides of 90 milliequiv. per liter, a diastase of 4 mg. and a nonprotein nitrogen of 54 mg. per 100 cc., a total protein of 5.9 gm., an albumin of 2.2 gm. and a globulin of 3.7 gm. per 100 cc. The icteric index was 10. The electrocardiogram showed left-axis deviation and premature auricular beats. An x-ray film of the gall-bladder region showed a shadow compatible with a distended gall bladder. X-ray study of the kidney and bladder regions was negative.

Five blood cultures made at various times during the hospital course were positive for *S. suipestifer* (European type). Three urine cultures were similarly positive, and of four stool cultures, one made a week after entry yielded the same organism. On entry, the blood serum agglutinated both the H and O antigens of *S. suipestifer* to a serum dilution of 1:40. A week later, the titer had risen to 1:1280 for both antigens.

During the first 6 days of the hospital course, the temperature fluctuated, with daily rises to a level between 102 and 104.5°F., often with chills (Fig. 1). On the 7th day, the administration of sulfathiazole was started, and although 32 gm. was given for 5 days, the temperature still remained high, with daily variations. On the 14th day, the temperature reached a peak of 105°F. Signs of consolidation appeared over the right lower lobe, and x-ray films showed marked cardiac enlargement, with diffuse clouding of the lungs, suggestive of pulmonary edema. At that time, sulfapyridine therapy was started, and a total of 20 gm. was given in 3 days. Because of the development of oliguria, hematuria and slight pitting edema, the drug was discontinued on the 3rd day. The temperature rose again, the signs of consolidation at the right base progressed, and abdominal distention, dyspnea and cyanosis appeared. Sulfapyridine therapy was again started on the 19th hospital day, and a total of 20.5 gm. was given in the course of 3 days. Although the temperature dropped somewhat, coarse rales appeared over both lung bases, generalized edema was noted, and the

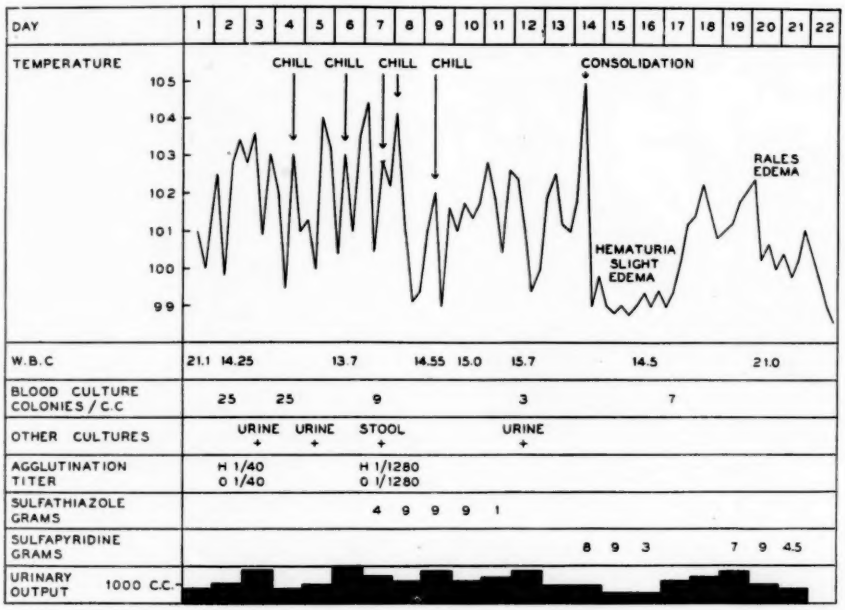

FIGURE 1. *Clinical Course in Case 1.*

The discharge diagnoses included *S. suipestifer* septicemia, *S. suipestifer* endocarditis (?), rheumatic heart disease, inactive, with aortic stenosis, and bronchopneumonia.

Autopsy. A post-mortem examination, limited to the neck, chest and abdomen, was performed on September 27, 1940, 4 hours after death. The pathological diagnoses included septicemia due to *S. suipestifer*, subacute bacterial endocarditis of the mitral valve caused by *S. suipestifer*, acute bronchopneumonia, pulmonary infarction (recent), focal hemorrhage and necrosis of liver, embolic nephritis, acute splenitis, rheumatic heart disease, myocardial fibrosis, stenosis and insufficiency of mitral and aortic valves, cardiac hypertrophy and dilatation, generalized arteriosclerosis, generalized congestion, pulmonary edema, hydropericardium, hydrothorax, dependent edema, pulmonary emphysema and atelectasis, and pulmonary infarction (old).

The heart weighed 560 gm. Its valve measurements were: tricuspid, 10 cm.; pulmonary, 7.5 cm.; mitral, 5 cm.; and aortic, 5 cm. The myocardium of the left ventricle measured 2.5 cm. in thickness, and that of the right ventricle 0.8 cm. The left ventricle was contracted,

and the left atrium, right ventricle and right atrium were dilated. The tricuspid and pulmonary valves were not remarkable. The mitral valve admitted only the little

FIGURE 2.

finger, and its cusps were markedly thickened. A large, soft, reddish vegetation measuring 1.5 by 1 by 0.5 cm. was attached to this portion of the posterior cusp (Figs. 2 and 3). Tiny, granular, friable vegetations were present along the entire line of closure of the mitral valve. The chordae tendineae were thickened and shortened. Plaques of calcified material were present on the ventricular surface of the anterior cusp. The aortic valve had rigid, thickened, roughened leaflets obstructing the lumen of the valve. Marked calcification was present in the aortic ring and extended upward into the leaflets. No gross vegetations were noted. The endocardium of the left atrium was somewhat thickened. The papillary muscles were hypertrophic, and the myocardium was pale red and markedly friable. The openings of the coronary arteries were somewhat narrowed by the marked arteriosclerotic processes in the sinuses of Valsalva. The coronary arteries were moderately tortuous, and their intima displayed numerous yellowish plaques.

On microscopic examination, the myocardium revealed a few small areas of fibrosis and scattered foci of cellular infiltration composed of lymphocytes, plasma cells, monocytes and polymorphonuclear leukocytes. A number of small recent hemorrhages were present without appreciable cellular response. The mural endocardium in one section was markedly thickened, consisting of hyaline connective tissue, with some infiltration of lymphocytes and plasma cells. Beneath the endocardium was a fairly wide zone of granulation tissue infiltrated with lymphocytes and polymorphonuclear leukocytes. The mitral valve revealed fibrosis, newly formed blood vessels and infiltration with polymorphonuclear leukocytes, lymphocytes, plasma cells and monocytes. Its atrial surface was covered by a large thrombus of fibrin enclosing cellular debris, red and white blood cells, and myriads of small gram-negative bacilli in large clusters (Fig. 4). The tissue immediately underlying the thrombus showed marked leukocytic infiltration and some fibroblastic proliferation.

Cultures taken during the post-mortem examination from the heart's blood, spleen and mitral vegetation were positive for *S. suipestifer* (European type).

CLINICAL FEATURES IN SUIPESTIFER ENDOCARDITIS

Except for the presence of bacterial endocarditis, the post-mortem findings in our case were compatible with those usually found in cases of suipestifer bacteremia. The pathology is that of a severe infection and frequently includes bronchopneu-

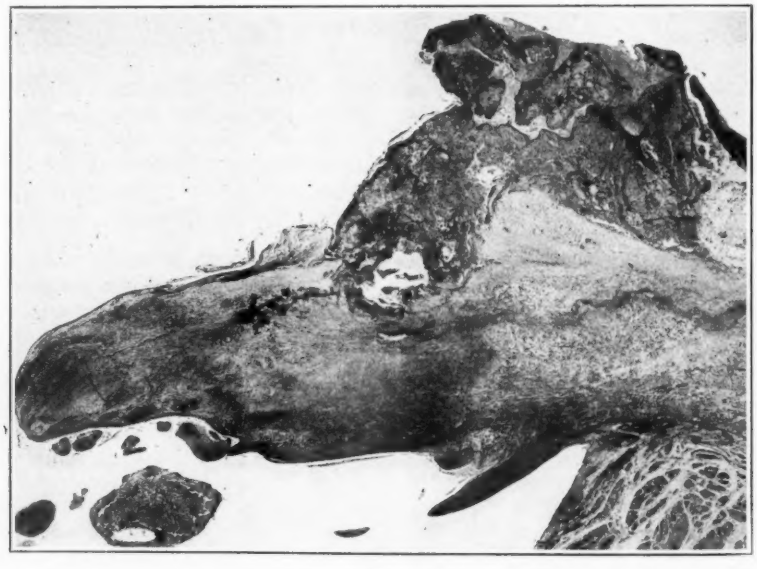

FIGURE 3.

monia, acute splenitis, focal necrosis of the liver and petechial hemorrhages. Pyarthrosis and osteomyelitis are not infrequent, and meningitis, pericarditis, cystitis, pyelonephritis and abscesses

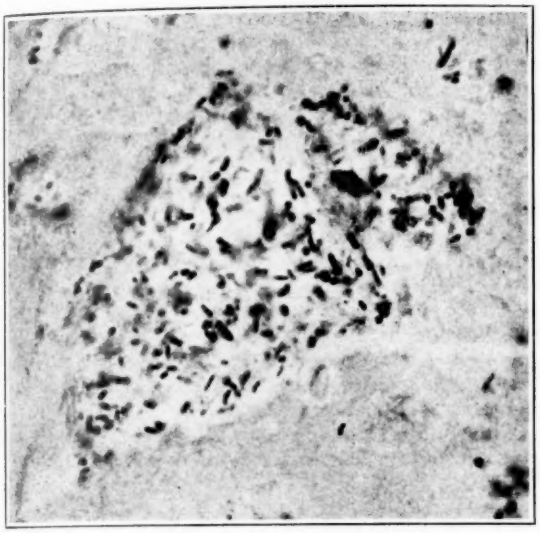

FIGURE 4.

in various parts of the body are found occasionally. To the list of unusual findings, bacterial endocarditis must be added.

The salient features of the 4 proved cases of bacterial endocarditis due to *S. suipestifer* are summarized in Table 1. In 3 cases, the endocarditis was superimposed on a valve already damaged, twice by rheumatic infection, and once by syphilis. Embolic phenomena were noted in 3 cases — in the skin, spleen, lungs, kidneys and brain. Clubbing of the fingers was absent. In no case was the spleen palpable. Fever was high and was associated with chills in all, and leukocytosis, an unusual finding in uncomplicated suipestifer bacteremia, occurred in all the cases. Changing murmurs were noted in 3 patients. Positive blood cultures were readily obtained, and in the only case in which it was mentioned, the agglutination titer was high. Chemotherapy with the sulfonamide drugs was attempted in 3 of the 4 cases, with no evidence that it had an appreciable effect on the course of the disease.

Thus, endocarditis due to *S. suipestifer* may occur and should be suspected whenever changing murmurs, leukocytosis and embolic phenomena are associated with a bacteremia due to this organism.

Other Cases of Suipestifer Infection in Boston

The appearance of this case of suipestifer endocarditis prompted a review of other cases of suipestifer infection seen in clinics co-operating with the Peter Bent Brigham Hospital.

*Suipestifer Infection in Children**

Six cases are reported from the Children's Hospital of Boston. These were all due to the European type of *S. suipestifer*. The fact that they are all fairly recent is probably due to more accurate bacteriologic classification than to an increased incidence of the disease.

TABLE 1. *Comparison of Four Cases of Suipestifer Endocarditis.*

Author	Age of Patient	Sex	White-Cell Count	Red-Cell Count	Type of Organism	Agglutinin Titer	Site of Lesion	No. of Positive Blood Cultures	Comment
	yr.		$\times 10^3$	$\times 10^6$					
Forster[14]	47	M	11.4–33.4	5.0	American	—	Right atrium, left ventricle	3	Patient, a Negro, had had syphilitic aortic insufficiency. Onset of acute and ulcerative endocarditis was insidious. Heart block and increasing systolic murmurs were noted. Hospital course lasted for 6 days.
	31	M	16.0–26.0	5.5–3.2	American	—	Mitral valve	7	Patient had had rheumatic fibrosis of mitral, aortic and tricuspid valves. Onset of acute, ulcerative endocarditis was insidious. Auricular fibrillation and inconstant diastolic murmurs were noted. Hospital course lasted for 21 days. Petechiae and infarcts were noted in spleen, kidney and lungs at autopsy.
Read[18]	49	F	11.7–20.0	5.5–3.9	European	—	Aortic valve	1	Onset of acute endocarditis was postoperative. Aortic systolic and diastolic murmurs were noted. Hospital course lasted for 66 days. Cerebral thrombosis was present.
Goulder, Kingsland and Janeway	58	F	13.7–21.0	4.5–2.7	European	H 1:1280 O 1:1280	Mitral valve	5	Patient had had rheumatic mitral and aortic stenosis and insufficiency. Onset of subacute endocarditis was sudden. Premature auricular beats and loud systolic murmurs were noted. Hospital course lasted for 22 days. Infarcts in kidney and lungs were found at autopsy.

CASE 2. J. V. (C. H. 178921), a 6-year-old boy, was admitted to the hospital on February 5, 1934, because of a 2-day episode of fever, vomiting and cough productive of

*We are indebted to the late Dr. Kenneth Blackfan, former physician-in-chief of the Children's Hospital, for permission to report Cases 2, 3, 4, 5, 6, 7 and 11 from the Children's and Infants' hospitals.

blood-streaked sputum. Physical examination revealed an acutely ill boy with numerous ecchymoses on the legs, inflamed tonsillar pillars, pharyngitis, signs of consolidation in the lower portion of the right upper lobe of the lungs and a palpable spleen. The white-cell count was 17,400, and the red-cell count was 4,550,000. A blood culture taken on the day of entry was positive for *S. suipestifer* (European type). The temperature rose to 106°F. on the 2nd day, and then gradually declined until it became normal on the 7th hospital day. During the first week, 2 stool cultures were positive for *Shigella paradysenteriae* (Sonne). The patient was therefore kept in the hospital for 23 days, to obtain a sufficient number of negative stool cultures. One month after discharge, the agglutination titer was 1:320 for the suipestifer H antigen, and 1:640 for the O antigen.

Case 3. D. G. (C. H. 189434), a 4-month-old boy, was admitted to the hospital on February 15, 1935, because of fever and diarrhea of 2 days' duration. Physical examination revealed a febrile, restless infant with pharyngitis and an inflamed left tonsil. The white-cell count was 15,000, and the red-cell count was 5,050,000. Several stool cultures were positive for *S. suipestifer* (European type), but blood cultures were negative. During the first few days, the patient had numerous loose greenish stools and ran a fever varying from 101 to 102.8°F. The temperature became normal on the 11th hospital day. On the 15th day, the spleen became palpable, but he was in such good condition that he was discharged 2 days later.

Case 4. T. W. (C. H. 190092), a 9-year-old boy, entered the hospital on March 18, 1935, because of abdominal pain, fever and delirium of 5 days' duration. Physical examination revealed pharyngitis, a palpable spleen and slurred speech. The white-cell count was 4400, and the red-cell count was 5,900,000. A lumbar puncture revealed normal spinal fluid. Blood cultures were positive for *S. suipestifer* (European type). The temperature ran from 99 to 100°F. for the 1st week. It then became normal, the patient's irritability subsided, and the spleen was no longer palpable. Before discharge on the 15th day, the agglutination titer was 1:320 for both H and O antigens.

Case 5. A. L. (C. H. 183420), a 6-year-old boy who had been treated in the Out-Patient Department for a meatal stricture, was admitted to the hospital on September 30, 1935, because of fever, anorexia and difficulty in passing urine. These symptoms began a week before entry and had gradually increased in severity. Physical examination was negative except for fever and a reddened glans with 2 meatal orifices. The white-cell count was 5400, and the red-cell count was 4,530,000. A blood culture was positive for *S. suipestifer* (European type). Both fever and urinary difficulty subsided by the 3rd day, and on the 7th day the patient was discharged.

Case 6. B. E. (C. H. 207904), a 2-year-old girl, entered the hospital on June 11, 1938, because of fever, marked sweating, vomiting and diarrhea of 24 hours' duration. Physical examination revealed a drowsy, apathetic, febrile child. The white-cell count was 6000, and the red-cell count was 4,800,000. A blood culture was positive for *S. suipestifer* (European type). The patient ran a high fever and leukopenia for the first 2 days, but the diarrhea promptly subsided. On the 3rd day, the temperature became normal, and the patient was no longer apathetic. She was discharged on the 10th day after three properly spaced stool cultures were reported negative.

Case 7. R. D. (C. H. 209725), a 2-year-old boy, was admitted to the hospital on June 10, 1939, because of fever and convulsions of 24 hours' duration. Physical examination revealed pharyngitis, rapid breathing and signs of consolidation in the right axilla. The white-cell count was 9600, and the red-cell count was 3,500,000. Two blood cultures were positive for *S. suipestifer* (European type). A lumbar puncture was negative. On the 1st day, the temperature reached a peak of 105°F. It gradually declined until it became normal at the end of the 2nd week. On the 5th hospital day, the liver and spleen became palpable. The patient was discharged on the 21st day.

These cases of suipestifer infection in children were all sporadic. The clinical picture was that of an acute infectious disease, which ran a febrile course of three to fifteen days. The age of the patients varied from four months to nine years, and with one exception all were males. Two cases had acute gastroenteritis with diarrhea. Pharyngitis was found in 4 patients, a palpable spleen in 3, and signs of pneumonia in 2. Only 2 patients had a definite leukocytosis. Of these, one had pneumonia and the other had acute gastroenteritis. Five had positive blood cultures; the one exception was a four-month-old child who had a positive stool culture. These data are summarized in Table 2.

Table 2. *Suipestifer Infection in Children.*

Case No.	Age	Sex	Duration of Fever	Pharyngitis	Pneumonia	Splenomegaly	Vomiting	Diarrhea	White-Cell Count	Red-Cell Count	Blood Culture	Stool Culture
	yr.		*days*						$\times 10^3$	$\times 10^6$		
2	6	M	8	+	+	+	+	—	17.4	4.6	+	—
3	1/3	M	12	+	—	—	—	+	17.8	5.1	—	+
4	9	M	12	+	—	+	—	—	4.4	5.9	+	—
5	6	M	10	—	—	—	—	—	5.4	4.5	+	—
6	2	F	3	—	—	—	+	+	6.0	4.8	+	—
7	2	M	15	+	+	+	—	—	9.6	3.5	+	—

Suipestifer Infection Complicating Parturition

Two cases of *S. suipestifer* infection occurred recently in women at the Boston Lying-in Hospital. In each case, the infection was due to the European type of the organism, and its source was unknown. Both newborn infants acquired the infection. One developed coryza, with a positive stool culture, and recovered; the other devel-

oped positive blood, spinal-fluid and stool cultures, and died.

Case 8. H. T. (B. L. H. 29220), a 21-year-old primipara, was admitted to the hospital on March 28, 1940, because of sharp pain in the right flank, radiating down the right thigh to the calf, of 24 hours' duration. Prior to admission, she had treated herself with local application of hot-water bottles to the right flank and had suffered second-degree burns. On admission, the temperature was 100.6°F., the pulse 86, the respirations 20, and the blood pressure 104/58. The patient seemed acutely ill, but tenderness in the right costovertebral angle was the only positive physical finding.

The urine contained 3 or 4 white blood cells per high-power field in the centrifuged sediment of a catheterized specimen. The hemoglobin was 40 per cent (Sahli), the red-cell count was 2,340,000, and the white-cell count 11,100. An x-ray film of the kidney region showed no evidence of stone. There was a total blood protein of 5.51 gm., an albumin of 2.98 gm., a globulin of 2.08 gm., and a nonprotein nitrogen of 34 mg. per 100 cc. Culture of the urine gave a growth of *Staphylococcus aureus* and hemolytic streptococcus.

During the next 2 days, the temperature rose to 104°F., and the patient experienced five chills during this period (Fig. 5). Blood cultures taken on March 28 and March 30 were positive for *S. suipestifer* (European type). Because of anemia, the patient was given a blood transfusion. On March 30, she went into labor and delivered a baby girl without particular difficulty. Because of persistent fever and signs in the left chest, an x-ray film was taken and interpreted as showing consolidation of the left lower lobe due either to pneumonia or more probably to pulmonary edema resulting from acute cardiac decompensation. Sulfapyridine was administered, and 18 gm. was given during the next 4 days without any demonstrable effect on the disease. Several attempts to isolate *S. suipestifer*, streptococci and pneumococci from the sputum were unsuccessful. The patient was given four more small blood transfusions, and the temperature fell to normal on the 10th hospital day; she made a rapid convalescence. On April 4, she began to complain of severe pain over the right sacroiliac region. On April 20, x-ray films showed slightly diminished radiance and roughening of the articular surface at the inferior border of the right sacroiliac joint. This pain disappeared after 2 or 3 weeks. Agglutination tests for *S. suipestifer* were positive to serum dilutions of 1:80 and 1:320 on April 1,

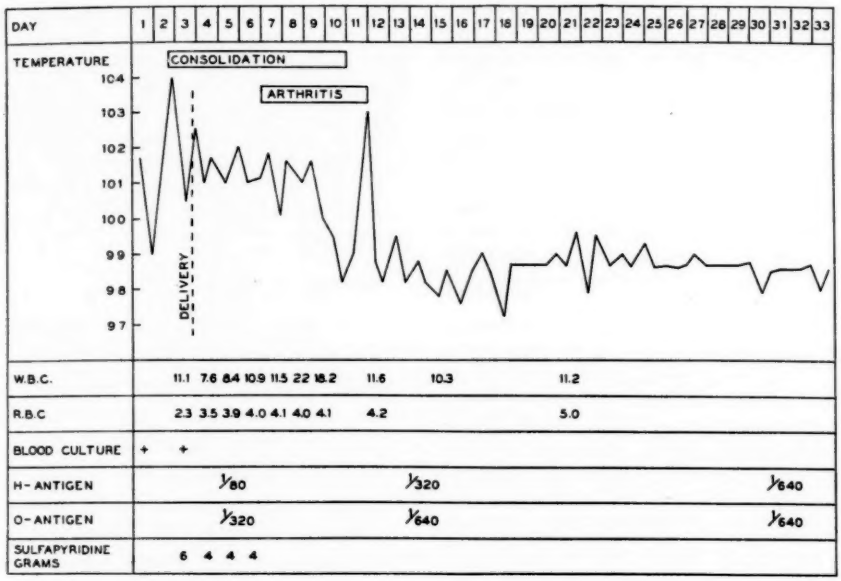

Figure 5. *Clinical Course in Case 8.*

of 1:320 and 1:640 on April 10 and of 1:640 and 1:640 on April 27 for the H and O antigens, respectively.

In a follow-up visit on August 15, the patient reported that she had been in good health since her discharge on April 29. The sacroiliac arthritis had not troubled her, and an x-ray film taken at that time showed definite narrowing of the joint and reaction in the bones on either side of the joint, apparently the end result of an inflammatory process. On April 16, 1941, O agglutination of *S. suipestifer* was negative, and H agglutination positive to a serum dilution of 1:160.

Case 9. Baby T. (B. L. H. 29220) was born on March 30, 1940, to the patient in Case 8 by a normal delivery. During the 1st week of life, the baby appeared ill, with poor color, cry and activity, and finally developed coryza and a fever reaching 100°F. A stool culture on the 20th hospital day gave a light growth of *S. suipestifer* (European type). Blood taken at the time of discharge on April 29 gave a positive agglutination for *S. suipestifer*, but all blood cultures were negative. A year later, the baby was seen and found to have normal weight and development.

Case 10. T. C. (B. L. H. 29171), a 23-year-old para III, who had lost her second child during an attack of eclampsia, was admitted to the hospital on April 13, 1940, 24 hours after delivery on the district service. During pregnancy, the patient was quite anemic. Delivery was by breech extraction, with forceps delivery of the after-coming head. During this process, the patient lost 300 cc. of blood. On the following day, the temperature rose

progressively to 103°F., with a pulse of 150, and hospitalization was therefore advised.

On admission, the patient appeared extremely pale and acutely ill. The temperature was 105°F., the pulse 136, and the respirations 30. Physical examination was otherwise negative.

The urine contained many gram-negative motile rods and 4 or 5 white blood cells per high-power field in the sediment. Examination of the blood showed a red-cell count of 1,770,000 with a hemoglobin of 30 per cent (Sahli), and a white-cell count of 7900. The stained blood smear showed marked variation in the size and shape of the red blood cells, and two nucleated red blood cells were noted. The total blood protein was 5.37 gm. per 100 cc. Cultures of the urine were positive for colon bacilli on three occasions. Two blood cultures were negative, but two out of eight stool cultures showed *S. suipestifer*. Agglutination tests with typhoid bacilli, paratyphoid A and B. bacilli, and *Brucella abortus* were negative, but on April 26 were positive for the H and O antigens of *S. suipestifer* (European type) to a serum dilution of 1:80. Agglutination of a strain of *Escherichia coli* from the stool was very slight.

The patient was given daily transfusions of 500 cc. of citrated blood for the first 6 days, and 1 cc. of concentrated liver extract daily from April 19 to April 23. The temperature, pulse and respirations fell gradually to normal by April 22. At discharge on May 7, the hemoglobin had risen to 84 per cent, and the white-cell count was 7500. Throughout the hospital course, the white-cell count fluctuated between 7900 and 2400.

The patient was seen again on April 16, 1941, when she stated that she had been in excellent health since a subtotal thyroidectomy in January, 1941, performed to relieve hyperthyroidism, which had developed soon after the termination of her pregnancy. At this time, no agglutinins for either the H or O antigen of *S. suipestifer* were detected in her blood.

Case 11. Baby C. (B. L. H. 23915), a male infant, was born at term on April 12, 1940, to the patient in Case 10 by breech extraction with forceps delivery of the head. The birth weight was 5 pounds, 6 ounces. At 24 hours, the patient was admitted to the Boston Lying-in Hospital with his mother, who was suffering from acute pyelonephritis due to *Esch. coli* and who was later found to harbor *S. suipestifer* in her intestinal tract. For 9 days, the baby appeared well, except for the persistence of jaundice and an episode on the 9th day when the temperature fell to 95°F. On April 22, the temperature rose to 100.8°F., and the patient appeared feeble, apathetic and hypoactive. The extremities were cold and cyanotic, the mucous membranes were pale, and the abdomen was distended. On April 23, the red-cell count was 4,400,000 with a hemoglobin of 75 per cent, and the white-cell count was 14,400. A blood culture was found to be positive for *S. suipestifer* (European type). Because of this infection, the patient was transferred on April 26 to the Infants' Hospital.

On admission, the baby was found to be poorly nourished and poorly developed, apathetic, jaundiced and slightly hyperpneic. The mucous membranes were pale, the abdomen was distended, and the spleen, kidneys and liver were palpable.

The urine sediment contained a few white blood cells and many granular casts per high-power field. The red-cell count was 3,300,000 with a hemoglobin of 80 per cent, and the white-cell count was 21,200. The blood Hinton reaction was negative, the icteric index 90, and the non-protein nitrogen 58 mg. per 100 cc. Lumbar puncture showed yellowish spinal fluid with a +++ test for globulin, normal sugar, a red-cell count varying from 450 to 5400, and a white-cell count varying from 12 to 92. The last included polymorphonuclear and mononuclear cells. Cultures of the spinal fluid, blood and stools were all positive for *S. suipestifer* (European type), but no agglutinins were found in the blood.

During the 7 days that the infant was at the Infants' Hospital, the temperature was constantly subnormal. Because of recurrent episodes of cessation of respiration, intracranial damage was suspected, and lumbar punctures were performed. The baby was given intravenous glucose and small transfusions, 10 gr. of sulfanilamide for the first 2 days and 63 gr. of sulfathiazole for the next 4 days. Despite all therapy, the patient died May 5, on the 21st day of life. Permission for an autopsy was not granted. The discharge diagnoses were *S. suipestifer* bacteremia and birth injury of the brain, with subarachnoid hemorrhage.

Summary of Cases

Two other cases of adult infections in Boston were reported in 1936 by Walker, Weiss and Nye.[16] Unlike the cases presented in this paper, these infections were due to the American type of *S. suipestifer*. In one case, a left subdiaphragmatic abscess developed in a twenty-three-year-old salesman who previously had experienced a severe illness characterized by fever, chills and diarrhea. The organism was cultured from the abscess when it was drained at operation. In the second case, a forty-year-old Negress had a cholecystectomy for chronic cholecystitis, and the organism was cultured from the gall bladder at operation.

To these cases, we now may add 11 more cases of sporadic infection due to the European type of *S. suipestifer*—6 cases in children, 2 in newborn infants, 2 in parturient women and 1 in an elderly woman. In this group, 2 deaths occurred—one in a newborn infant, who developed both bacteremia and meningitis, and the other in the elderly woman, who developed bacterial endocarditis. Since the ages ranged from the newborn period to fifty-eight years, there appears to be universal susceptibility to infection of this type. All the patients had high fever, ranging in duration from eight to thirty-eight days. Eight patients had positive blood cultures; the other 3 had positive stool cultures. The patient with bacterial endocarditis had positive stool and urine cultures, in addition to positive blood cultures. The composite clinical picture included chills and fever, coryza and pharyngitis, pneumonia, splenomegaly, abdominal pain, vomiting, diarrhea, arthritis, meningitis and bacterial endocarditis. In uncomplicated bacteremia, the white-cell count tended to remain low, but once localization of the infection occurred, leukocytosis usually developed.

Laboratory Diagnosis of Suipestifer Infections

The diagnosis of infection due to *S. suipestifer* is made by isolation of the organisms, which can most frequently be done by blood culture and less frequently by stool or urine culture. Once isolated, these organisms are readily identified as members of the paratyphoid group by their morphology (gram-negative bacilli), motility, fermentation of dextrose, with the production of gas, and inability to ferment lactose.

Further identification depends on the use of special tests, both fermentative and serologic. *S. suipestifer* is distinguished from all the other Salmonella organisms by its inability to ferment arabinose. Its inability to ferment inositol and trehalose may be used as confirmatory evidence. It is distinguished in this manner from *S. hirschfeldii* (paratyphoid C bacillus, also known as the Eastern type of *S. suipestifer*) which ferments arabinose, usually trehalose, but not inositol. The American and European types, known as *S. suipestifer* and *S. suipestifer var. kunzendorf* respectively, are separated on the basis of hydrogen sulfide production, which can best be tested by the use of Kligler's iron agar. The European type produces hydrogen sulfide, which gives black colonies on Kligler's agar, whereas the American type does not.

Although these biochemical reactions justly deserve an important place in the classification of the gram-negative bacilli, most laboratories make use of agglutination tests with stock antiserums to confirm the tentative identification made by sugar fermentations. The accuracy and specificity of agglutination tests in this large group of morphologically similar organisms have been enormously enhanced by the work of White and of Kauffmann,[17] whose painstaking antigenic analyses carried out with carefully absorbed serums have resulted in the so-called "Kauffmann–White scheme of classification."

Weil and Felix[18] first introduced the terms "H" and "O" as applied to motile and nonmotile variants of a culture, H standing for *Hauch* (flagella), O for *ohne Hauch* (without flagella). H agglutinins are antibodies to the antigens of the flagella of the bacteria, and their union with the flagella results in the formation of loose clumps and prompt immobilization of the motile bacteria. Thus, H agglutination becomes readily visible within two hours at 55°C. as large, coarse floccules, or microscopically is visible almost instantly as an immobilization of the bacteria with the formation of loosely tangled groups of organisms. On the other hand, the O or somatic agglutinins are directed to the antigens of the cell bodies. If the organisms are motile, or if the flagella are preserved as in a formalinized suspension, O agglutination does not occur, because H agglutination occurs first. However, if the flagella are removed by chemical treatment, or by the production of a nonmotile variant, O agglutination can be demonstrated. Since the bacterial bodies are sensitized, tight packing of the bacteria takes place as agglutination proceeds. Consequently, the clumps formed are small, and it takes six to twelve hours at 55°C. for macroscopic agglutination to occur. H suspensions are either live mo-

Table 3. *Classification of the Commoner Salmonella Organisms.**

Salmonella Group	Organism: Official Name	Organism: Other Name or Names	Somatic Antigens: Major	Somatic Antigens: Minor	Flagellar Antigens: Specific Phase	Flagellar Antigens: Group Phase
A	*S. paratyphi*	Paratyphoid A bacillus	I	II	a	—
	S. species (Newcastle or Senftenberg type)	Newcastle bacillus	I	III	gs	—
B	*S. schottmuelleri*	Paratyphoid B bacillus	IV, XII	V	b	1, 2
	S. typhi murium	Mouse typhoid bacillus; *Bact. aertrycke*; *B. pestis caviae.*	IV, XII	V	i	1, 2, 3
C	*S. hirschfeldii*	Paratyphoid C bacillus; *S. suipestifer*, Eastern type.	VI	VII	c	1, 4, 5
	S. cholerae suis	*S. suipestifer*, American type; hog cholera bacillus.	VI	VII	c	1, 3, 4, 5
	S. cholerae suis (Kunzendorf type)	*S. suipestifer var. kunzendorf*; *S. suipestifer*, European type.	VI	VII	—	1, 3, 4, 5
	S. species (Newport type)		VI	VIII	eh	1, 2, 3
D	*S. enteritidis*†	Gaertner's bacillus	IX, XII	—	gom	—
E	S. species (London type)	Salmonella, Type L	III, X	—	lv	1, 4, 6
F	S. species (Aberdeen type)	*Bact. aberdeen*	XI	—	i	1, 2, 3
G	S. species (Poona type)	*Bact. poona*	XIII	—	z	1, 4, 6
I	S. species (Hvittingfoss type)		XVI	—	b	—

*There are many other organisms in Groups B, C and D, a total of 68 being listed in the last edition of Bergey's *Determinative Bacteriology*.

†The typhoid bacillus (*Eberthella typhosa*) although not strictly a Salmonella organism, is antigenically a member of Group D, with an antigenic formula 9, 12:d:–. It is always in the specific phase.

tile cultures or formalinized suspensions. O suspensions are prepared from a nonmotile variant or by treating a culture of a motile organism with 50 per cent alcohol for twenty-four hours, or with a temperature of 100°C. for 15 minutes, either of which procedures destroys the H antigens. H agglutination tests are read after two hours at 55°C. and refrigeration overnight; O agglutination tests are read after six hours at 55°C. and refrigeration overnight.

The Kauffmann–White classification[19, 20] divides the Salmonella organisms into eight different groups on the basis of their O or somatic antigens, which are conventionally represented with Roman numerals. The different species within the groups are separated on the basis of their H or flagellar antigens, for which small letters are used, or, in some cases, on the basis of minor O antigens. Unfortunately, many of these organisms can exist in two phases. In the specific phase, an organism possesses flagellar antigens peculiar to itself, but in the group phase the flagellar antigens are common to many other members of the Salmonella group. These group H antigens are represented by Arabic numerals. Table 3 gives the antigenic formulas for the commoner members of the Salmonella group, arranged according to Kauffmann's scheme, with the various names used for the different species.

It will be noted that *S. suipestifer* (American type) can exist in both group and specific phases, whereas *S. suipestifer var. kunzendorf* (European type) can exist only in the group phase. Thus, when the former is in the group phase, it cannot be distinguished from the latter by agglutination, and the test for hydrogen sulfide production must be used.

When all this is known, it becomes apparent that the use of the agglutination reaction is beset with pitfalls unless one knows what phase the antigens are in and what phase the organism was in when injections were made to produce the diagnostic serum. If only H agglutination is used, mistakes may be frequently made. For example, the antigenic formula for *S. schottmuelleri* (paratyphoid B bacillus) is IV, XII, V : b : 1, 2, and that for *S. typhi murium* is IV, XII, V : i : 1, 2, 3. These two organisms are among the most frequent to be isolated from Salmonella infections in this area. If an organism is isolated that seems to belong to the Salmonella group, it would probably be tested first in serum made against *S. schottmuelleri*. If the serum were made with organisms in the group phase, it would contain antibodies to the group flagellar antigens 1 and 2. If the unknown organism happened to be *S. suipestifer var. kunzendorf*, which is always in the group phase, it would agglutinate to a marked extent, because its flagellar antigens are 1, 3, 4 and 5, the first of which it shares with *S. schottmuelleri*. This confusion can be straightened out by fermentation tests with arabinose and trehalose, both of which are fermented by *S. schottmuelleri* and not by *S. suipestifer*. Furthermore, if the unknown culture is heated to boiling for half an hour to destroy the H antigens, it can then be retested as an O suspension. Under these conditions, it will agglutinate only in a serum made against a member of Group C, which contains somatic antigens VI and VII. This is a very useful procedure, which we have had to use in completing the identification of the organisms isolated from some of the cases reported in this paper, since they gave H agglutination in both our stock suipestifer and paratyphoid B antiserums.*

It is therefore quite obvious that the final identification of many Salmonella strains is beyond the scope of the ordinary hospital laboratory. On the other hand, the Salmonella Center† in New York City is equipped for antigenic analysis, and strains may be sent there for identification. Although this procedure seems like a rather academic matter, it is of great epidemiologic interest to identify as many strains as possible, so that data on the distribution and mode of spread of these organisms may be obtained.

Next to a blood culture, the agglutination test is most useful in making a diagnosis of this type of infection, and should be used in cases of obscure fever. In Harvey's[3] series of cases, 88 per cent gave positive agglutination reactions by the fourth week of the disease. It is essential to get serum from a patient early in the disease, so that it may serve as a control for later tests, which may show positive reactions.

To ascertain the value of the agglutination test in the diagnosis of *S. suipestifer* infection in the Boston area, we have studied a considerable number of serums. We have used both H and O antigens, the former prepared by formalinizing an eighteen-hour culture of the European type of *S. suipestifer* (group phase), and the latter by a twenty-four-hour treatment of the culture with 50 per cent alcohol. From what has already been said, a positive O agglutination would be expected following any infection caused by a member of Group C, and a positive H agglutination would occur after infection with any organism of the

*Subsequent antigenic analysis of the paratyphoid B strain from which our stock antiserum was made has shown that it has organisms in both the group and the specific phases, which accounts for the lack of specificity of our paratyphoid B antiserum and antigen.

†The Salmonella Center, Beth Israel Hospital, New York City, corroborated our bacteriologic diagnosis in Cases 1, 8 and 9.

Salmonella group that happened to be in the group phase and to contain any of the flagellar antigens 1, 3, 4 and 5. In typhoid infection, it is believed that O agglutination is of more significance than H agglutination, since the latter may be increased as a result of prophylactic inoculation, whereas the titer of the former rises less with immunization but may go very high with infection.

We studied a number of normal serums to determine whether agglutinins for *S. suipestifer* were present. A similar study was made with serums taken from patients six weeks after immunization with typhoid-paratyphoid B vaccine. Since none of these serums showed any significant degree of agglutination with either the H or O antigen, it must be assumed that a positive agglutination test for *S. suipestifer* has considerable significance in this locality. However, since our patients with suipestifer infections developed equally high titers of H agglutinins for *S. suipestifer* suspensions and for our stock suspension of *S. schottmuelleri* (paratyphoid B bacillus),* H agglutination is not specific. But when titers for both H and O agglutinins are found to be elevated, we consider it diagnostic of infection with *S. suipestifer* or a related organism in Group C.

Another important question concerns the persistence of agglutinins following infection with this organism. We were able to obtain serums from 6 patients who had had their infections from one to six years previously.

The data on these cases and on all the agglutination tests are summarized in Tables 4 and 5.

The Widal test, as ordinarily done, consists in testing an unknown serum against suspensions of typhoid and paratyphoid A and B bacilli. It is much more sensible to adapt it to the needs of the locality. In the Boston area, the commonest Salmonella infections are due to *S. schottmuelleri* (*Bact. paratyphosum B*), *S. typhi murium* and *S. suipestifer var. kunzendorf*, so that suspensions of these organisms should be used in the Widal test. The inclusion of a suspension of *S. suipestifer var. kunzendorf* has the added advantage of being in the group phase and, thus, of being able to detect antibodies to the group phase of almost all members of the Salmonella group. The other suspensions should be in the specific phase. We include a single O suspension, usually prepared from typhoid bacilli, in our Widal test, since there is some evidence that O antibodies are less specific in man than in rabbits. Moreover, O antibodies may occasionally develop in typhoid fever without H antibodies.

TABLE 4. *Results of Agglutination Tests with Serums from Normal Subjects and Those Immunized with Typhoid-Paratyphoid B Vaccine.*

SERUM	NUMBER OF SUBJECTS	SERUM DILUTION TITERS			
		TYPHOID H	PARATYPHOID B H	SUIPESTIFER H	SUIPESTIFER O
Normal subjects	34	—	—	0	0
Immunized subjects	4	1:160	1:80	1:10	0

SUMMARY AND CONCLUSIONS

From a survey of the literature, it is apparent that *Salmonella suipestifer* infection occurs in epidemic form as acute food poisoning, with low mortality, and in endemic form at any age, with a considerable mortality, because it often complicates some debilitating disease. These latter cases are characterized by fever, frequently leukopenia, bacteremia and a tendency for the infection to localize in the bones, joints or lungs.

TABLE 5. *Persistence of Agglutinins after Suipestifer Infection.*

CASE NO.	PERIOD AFTER INITIAL INFECTION	AGGLUTININS	RESULTS IN VARIOUS SERUM DILUTIONS						ORIGINAL TITER
			1:10	1:20	1:40	1:80	1:160	1:320	
	yr.								
2	6	H	+++	++	+	0	0	0	1:320
		O	+	0	0	0	0	0	1:640
4	5	H	++++	++++	+++	++	+	±	1:320
		O	++++	++++	+++	++	+	0	1:320
5	5	H	++++	+++	+	0	0	0	—
		O	0	0	0	0	0	0	—
7	1½	H	++++	+++	+++	+++	+	0	—
		O	+	+	+	±	0	0	—
8	1	H	++++	++++	+++	+++	±	0	1:640
		O	0	0	0	0	0	0	1:640
10	1	H	+	0	0	0	0	0	1:80
		O	0	0	0	0	0	0	1:80

\+ = minimal positive agglutination.
++++ = maximal positive agglutination.

*See first footnote on page 136.

Eleven cases of sporadic infection occurring in the vicinity of Boston during the past six years are reported.

The clinical course and post-mortem findings in a fatal case of bacterial endocarditis due to *S. suipestifer* in a fifty-eight-year-old woman with rheumatic valvular disease are described.

The bacteriologic diagnosis of this infection is discussed. A positive blood culture most frequently reveals the diagnosis, occasionally a positive stool or urine culture. *S. suipestifer* is identified as a paratyphoid bacillus that does not ferment arabinose.

The significance of the agglutination reaction in this infection is discussed. Agglutinins for *S. suipestifer* were not found in normal serums, nor in the serums of patients immunized with typhoid-paratyphoid B vaccine. High agglutination titers were found in the serums of most patients with suipestifer infection, and these persisted for periods varying from a few months to six years after infection in a small group of cases.

The importance of using standard antigens and properly prepared antiserums in the identification of the various Salmonella types is pointed out.

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THE ACTION OF FURMETHIDE (FURFURYL-TRIMETHYL-AMMONIUM IODIDE) ON THE BLADDER IN PATIENTS WITH URINARY RETENTION FOLLOWING SURGERY ON THE RECTUM*

Preliminary Report

JOSEPH H. LIPTON, M.D.,† SAMUEL B. BEASER, M.D.,‡ AND MARK D. ALTSCHULE, M.D.§

BOSTON

A NUMBER of parasympathomimetic drugs, such as Mecholyl and Doryl, are known to cause contraction of the bladder, but untoward side effects limit their clinical use. A new parasympathomimetic drug, Furmethide (furfuryl-trimethyl-ammonium iodide), has been found to have a strong action on the bladder and relatively little effect on the cardiovascular or gastrointestinal system, so that distressing side reactions are not common following its use in the treatment of the atonic bladder. The action of Furmethide is being studied at present in a wide variety of bladder atonies, including those associated with diabetes, lesions of the spinal cord, postoperative states and trauma to the bladder. Since a complete evaluation of the effectiveness of the drug will require many months, it is considered desirable to call attention to its usefulness by describing its action in one of the syndromes studied, that is, urinary retention following operations on the rectum.

*From the Medical Research Laboratories and the Medical, Urologic and Surgical services, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

This investigation was aided by a grant from Smith, Kline and French Laboratories, Philadelphia.

†Resident in urology, Beth Israel Hospital.

‡Assistant in medicine, Harvard Medical School; junior visiting physician, Beth Israel Hospital.

§Associate in medicine, Harvard Medical School; associate visiting physician, Beth Israel Hospital.

Material and Methods

All patients, excluding those with prostatic obstruction, subjected to abdominoperineal operations for carcinoma of the rectum during the period of this study were observed. They were placed on constant catheter drainage for ten to fourteen days after operation, or until they were

ambulatory. Intermittent catheterization was employed following removal of the tube. No treatment was given if the volume of residual urine was small. If, however, it was greater than 300 cc., or if the patient could not void spontaneously, treatment with Furmethide was begun. This report is based on the results in 3 consecutive cases. Twelve patients with normal uninfected bladders were used for control studies.

A continuous flow-recording cystometer of the type described by Prien[1] was used; previous studies by one of us (J. H. L.) had demonstrated its sensitivity and accuracy. The patient was placed in the recumbent position and, after he had voided, was catheterized; control cystometric measurements were made of vesical pressure during filling, first desire to void, slight discomfort or fullness, severe discomfort or fullness, maximal voluntary pressure and vesical capacity. Furmethide was then given subcutaneously in doses of 3 to 5 mg. Within five minutes, mild salivation, sweating, a feeling of warmth and a desire to void occurred. A second series of cystometric measurements was begun at this time. The effects of the injection of Furmethide on the bladders of the 12 control subjects are summarized in Table 1 and Figure 1.

TABLE 1. *Average Effect of 5 Mg. Furmethide on Cystometric Measurements in 12 Normal Subjects.*

OBSERVATION	BEFORE DRUG	AFTER DRUG
Vesical pressure	11–17 cm. water	25–52 cm. water
First desire to void	150 cc.	40 cc.
Slight discomfort or fullness	400 cc.	50 cc.
Severe discomfort or fullness	410 cc.	55 cc.
Maximal voluntary pressure	70 cm. water	80 cm. water
Vesical capacity	410 cc.	75 cc.

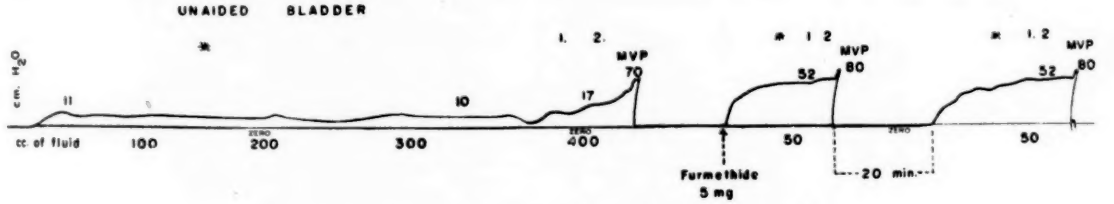

FIGURE 1. *Effect of Furmethide on the Normal Bladder. The asterisks indicate the first desire to void.*

CASE REPORTS

CASE 1. A 64-year-old man was subjected to a one-stage abdominoperineal resection of an adenocarcinoma of the rectum on May 24, 1941. The tumor was found to be fixed to the base of the bladder, which was accordingly mobilized extensively and its serosa stripped away. Constant urinary drainage was begun after operation and continued until June 8, after which the patient voided only in small amounts and was found to have 400 cc. of residual urine; cystometric studies showed normal vesical pressure during filling, first desire to void at 400 cc. and a vesical capacity of 425 cc. After the administration of 5 mg. of Furmethide subcutaneously, a marked increase in vesical pressure during filling occurred (Fig. 2), with first desire to void at 40 cc. and a vesical capacity of only 50 cc. A second determination yielded similar results. Sweating, lacrimation and salivation occurred. The next day, 4 mg. was given subcutaneously; 300 cc. of urine was voided spontaneously within 10 minutes, and the residual urine volume was only 75 cc. Voiding of small amounts continued during the day. On June 10, the administration of 3.0 mg. subcutaneously resulted in spontaneous voiding, with a residual urine volume of 20 cc. On the next day, the drug was not given, and the residual urine increased to 150 cc. On June 12, the drug was given orally, in doses of 10 mg., twice during the day; the patient voided well and the residual urine volume was only 20 cc. The drug was discontinued on June 14, and at the time of discharge 5 days later, the residual urine volume was still only 50 cc.

CASE 2. A 67-year-old man was subjected to a one-stage abdominoperineal resection of an adenocarcinoma of the rectum on March 4, 1941. Constant catheter drainage was continued until March 17, after which intermittent catheterization repeatedly yielded 450 cc. of residual urine. Cystometric studies 5 days later showed normal tension, first desire to void at 300 cc., and a vesical capacity of 400 cc. (Fig. 3). The administration of Doryl subcutaneously, from March 18 to 22, did not appreciably affect bladder function, the residual urine volume ranging between 150 and 380 cc. The administration of 5 mg. of Furmethide subcutaneously caused a marked increase in vesical pressure during filling, with desire to void at 90 cc. and a vesical capacity of 140 cc. (Fig. 3). On March 23, 3 mg. of the drug was given subcutaneously, after which the patient voided 350 cc. and was found to have only 100 cc. of residual urine. On the following 2 days, no drug was given, and 425 cc. of residual urine was found repeatedly. Beginning on March 26, the drug was given orally in doses of 10 mg. three times a day. Spontaneous voiding was maintained, and the volume of residual urine decreased to 20 cc. on March 30. At the time of discharge on April 3, the residual urine was still less than 30 cc.

CASE 3. A 45-year-old man was subjected to a one-stage abdominoperineal resection for adenocarcinoma of the rectum on May 23, 1941. Constant catheter drainage was employed until June 6, after which the volume of residual urine ranged between 400 and 900 cc. Cytometric studies on June 13 showed a neurogenic-bladder curve, with first desire to void at 800 cc. and a vesical capacity of 850 cc. After the administration of 5 mg. of Furmethide subcutaneously, there was an increase in vesical pressure during filling, with first desire to void at 100 cc. and a

vesical capacity of 150 cc. (Fig. 4). On a regime of 5 mg. of the drug subcutaneously, twice daily, the volume of residual urine decreased to 150 cc. On June 18, the drug was started orally, in doses of 25 mg. twice daily, and the residual urine volume rapidly decreased to 40 cc. The patient was discharged, with orders to continue that dosage; on July 9, the volume of residual urine was 50 cc., and cystometric studies yielded essentially normal results, with first desire to void at 210 cc. and a vesical capacity of 280 cc. The drug was discontinued, and on July 23 the residual urine volume was 250 cc. Resumption of oral Furmethide therapy reduced the volume of residual urine to 40 cc.; withdrawal of the drug resulted in an increase to 250 cc. on September 18, with first desire to void at 325 cc. and a vesical capacity of 500 cc. Since that time, the patient has been taking 10 mg. of Furmethide by mouth twice daily. He empties his bladder almost completely, the stream is full, and he has no urinary symptoms. He experiences only mild sweating and a feeling of warmth after taking the drug.

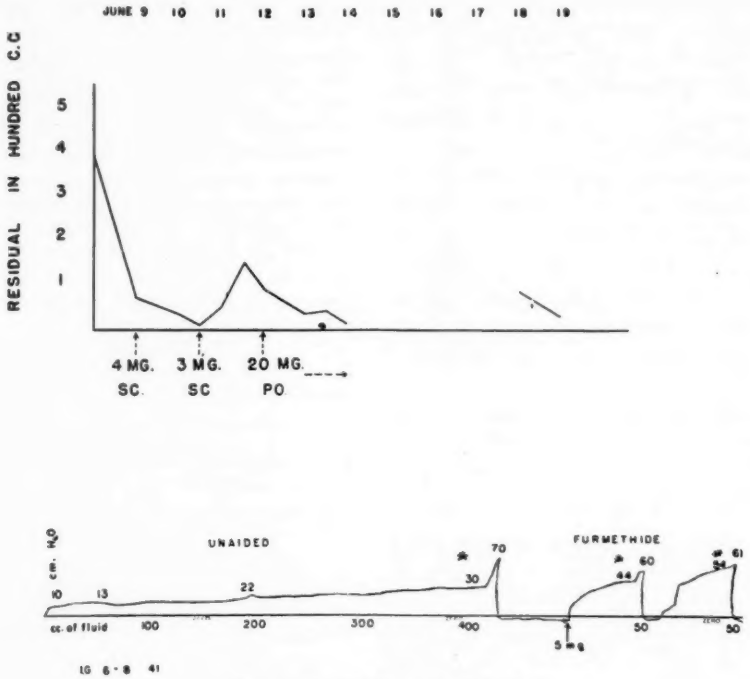

FIGURE 2. *Findings in Case 1.*

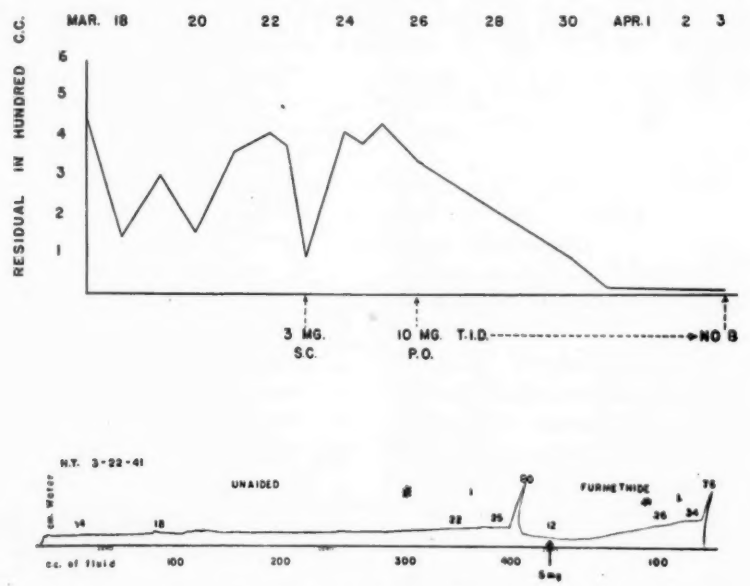

FIGURE 3. *Findings in Case 2.*

DISCUSSION

The importance of urologic complications following major operations on the rectum has been

stressed by Ewert[2] and by Seaman and Binnig.[3] Ewert found 219 cases of urologic disturbance among 750 cases with operations on the colon, 75 per cent of them in patients after rectal surgery; some of the patients required tidal drainage for periods of one to three months. Seaman and Binnig[3] also reported the frequent need for tidal drainage following resection of the rectum and mentioned attempts to control the symptoms by means of the injection of Mecholyl and ergotamine tartrate. A similarly high incidence of urinary complications after abdominoperineal resection has been observed at the Beth Israel Hospital. It was believed that bladder dysfunction after resection of the rectum was probably due to detrusor atony resulting from damage of the parasympathetic nerve supply of the bladder, and that the administration of parasympathomimetic drugs might therefore control the symptoms. The employment of Mecholyl and of Doryl having proved generally unsatisfactory, the clinical uses of Furmethide, previously shown by other authors[4–6] to have somewhat similar pharmacologic effects, was therefore considered. The effective manner in which the administration of Furmethide has been found to control bladder dysfunction following major operations on the rectum is clearly exemplified by the findings in the cases described.

When Furmethide is given in doses of 3 mg. subcutaneously or 10 mg. by mouth, the side reactions consist only in slight sweating and a feeling of warmth. With somewhat larger doses, these symptoms are more marked, and salivation is pronounced. Still larger doses, that is, 10 mg. subcutaneously or 30 mg. by mouth, cause severer discomfort and may also give rise to nausea and vomiting. In all cases studied thus far, however, it has been possible to find a dose of the drug that is effective in its action on the bladder and does not cause significant discomfort because of the side effects.

The chemical similarity of Furmethide to Mecholyl and Doryl is based on the fact that all contain a trimethyl ammonium halide group (Fig. 5). Furmethide differs from the other two pharmacologically in that its action on the heart and lungs

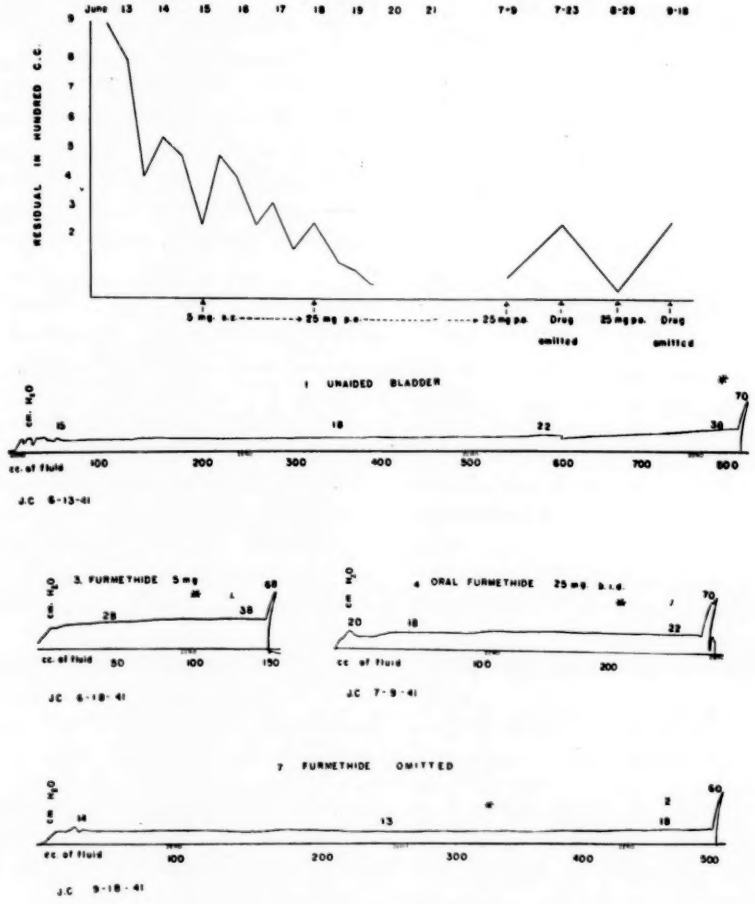

FIGURE 4. *Findings in Case 3.*

is weaker than that of Mecholyl, its action on the gastrointestinal tract is weaker than that of Doryl, and its action on the bladder is consid-

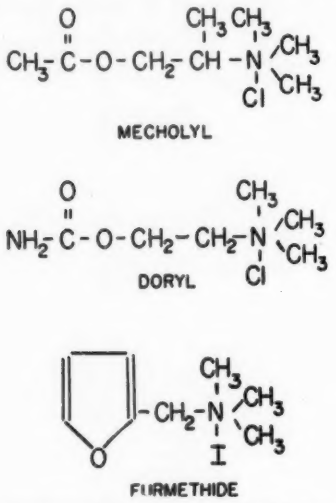

FIGURE 5. *Structural Formulas of Mecholyl, Doryl and Furmethide.*

erably stronger than both. The advantages of these properties for the control of atony of the bladder are clear.

SUMMARY AND CONCLUSIONS

The action of Furmethide (furfuryl-trimethyl-ammonium iodide) on the normal bladder and on the bladder that has become atonic after major operations on the rectum is described. Its effect is to increase tone, restoring it in atony to or toward normal. The drug has been used effectively in the control of bladder dysfunction in 3 cases after abdominoperineal resection of carcinoma of the rectum. Although discomfort due to side reactions may be appreciable after administration of large doses of Furmethide, in clinical usage it has been possible to find a dose that is effective in its action on the bladder and does not cause significant discomfort because of the side effects.

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PRIMARY ADENOCARCINOMA IN A MECKEL'S DIVERTICULUM

HOLLIS L. ALBRIGHT, M.D.,* AND JOHN S. SPRAGUE, M.D.†

BOSTON

INCREASING attention is being directed to Meckel's diverticulum, as judged by the reports in the literature of collected rather than single cases. The diverticulum has been estimated to be present in 2 per cent of all adults (Nygaard and Walters,[1] and Skinner and Walters[2]). It is usually observed as an incidental finding either at operation or at post-mortem examination. Symptoms do not usually arise until pathologic changes have taken place in the diverticulum. The complications are frequent, varied and almost always severe, and are of prime clinical importance; they may lead in some cases to an acute surgical emergency, and in others to a belatedly recognized cause of death. Attention is directed here to neoplastic disease of the diverticulum, particularly carcinoma.

Normally, the yolk stalk (omphalomesenteric duct), which connects the alimentary canal with the yolk sac, becomes closed during the fifth week of fetal life. Failure of this duct to become completely obliterated may lead to any one of four anomalies. If the duct remains entirely open, an intestinal fistula results, with discharge of ileal contents through the umbilicus; this differs from a patent urachus because of the discharge of feces rather than urine. Secondly, if the duct remains open throughout its distal portion, an umbilical fistula results, with active secretion from its glandular lining. Thirdly, if the duct becomes obliterated at both ends but fails to close in the middle, a retention cyst or true enterocystoma forms, requiring surgical removal. Fourthly, if only the distal end closes and the ileal end remains open, a true Meckel's diverticulum results.

There are several distinguishing characteristics of a Meckel's diverticulum. It is usually located from 25 to 100 cm. from the cecum, almost always on the antimesenteric border. According to Reiser,[3] the wall usually lacks the circular mus-

*Instructor in surgery, Boston University School of Medicine; visiting surgeon, Massachusetts Memorial Hospitals.

†Assistant in surgery, Boston University School of Medicine; second assistant visiting surgeon, Massachusetts Memorial Hospitals.

culature. When all the layers of normal intestine are present, the diverticulum may actively discharge its contents. In the case reported here, the diverticulum was 1 cm. away from the mesenteric border. The neck may vary widely in size, from the usual broad sessile type to the very narrow, as in our patient. A very narrow opening into the ileum may lead to impaction and decomposition of the diverticular contents. This may explain why preoperative x-ray studies with barium fail to disclose the diverticulum.

Histologically, the diverticulum is usually lined with ileal mucosa. In approximately 25 per cent of the cases, however, heterotopic mucosal variations have been observed. Typical mucosas of the gastric or jejunal types and pancreatic tissue are the chief variants seen. Gastric mucosa occurs oftenest at the neck of the diverticulum, and it is thought that the secretion of hydrochloric acid by the mucosal glands disposes to erosion, ulceration and hemorrhage at this site.

Pathologic changes, occurring in 25 to 33 per cent of the cases (Nygaard and Walters[1]), may be described as mechanical, inflammatory, heterotopic and neoplastic. The contents may undergo decomposition, especially if the neck of the diverticulum is narrow. Gangrene and obstruction may result from volvulus or invagination of the diverticulum into the ileum to cause intussusception. Inflammatory changes may predominate, as in idiopathic diverticulitis with regional peritoneal irritation, and in later stages, perforation and diffuse peritonitis. Peptic ulcer arising in aberrant gastric mucosa is the more prominent disturbance associated with heterotopic tissue formation. The ensuing intestinal hemorrhage may be depleting and severe. Neoplastic changes in the diverticulum have been observed in the form of myoma, lipoma, neuroma, papilloma and carcinoid as benign growths, and sarcoma and carcinoma as malignant growths, with and without metastases to the mesenteric nodes.

The greater number of diverticulums are uncomplicated, cause no symptoms, and are found incidentally at operation or autopsy; they rarely contain heterotopic tissue. The varied complications give rise to no single, characteristic syndrome. Nevertheless, a revealing, more or less definite symptom complex may be seen in the major types of lesions. Pain, soreness or tenderness is present in approximately 50 per cent of the cases. The pain is usually intermittent, colicky and moderate, and occurs chiefly in the right lower abdomen. The tenderness is often localized to the right or left of the umbilicus.

Symptoms of obstruction have arisen more commonly from intussusception and adhesive bands, either inflammatory or connecting the diverticulum to the umbilicus, thus obstructing a loop of adjacent bowel. Volvulus is much less common. Over 170 cases of intussusception due to an invaginated Meckel's diverticulum have been collected and reported (Harkins[4] and Greenblatt et al.[5]). In addition, inflammatory lesions may lead to adhesions between the diverticulum and bowel, resulting in obstruction.

The symptomatology of the diverticulitis group simulates that of appendicitis, except that the tenderness has often been localized at or to the left of the umbilicus. Unless the appendix has been previously removed, it may be impossible to differentiate diverticulitis from appendicitis. This will not delay the institution of proper treatment, however, for such a syndrome should lead to early surgical intervention in both situations.

The peptic group[6] may simulate the peptic-ulcer syndrome, the symptoms depending on the presence of ulceration, hemorrhage or perforation, with peritonitis. Intestinal hemorrhage has been found to be the essential finding, and often the only one, of this group. Acute anemia may result. Vague to definite periumbilical pains, often related to meals and associated with past or recurring intestinal hemorrhage, suggest the diagnosis. Not every case of ulceration has hemorrhage, perforation or pain, yet all three may be present.

The chief symptoms arising from an umbilical fistula are soreness, tenderness and a mucopurulent or fecal discharge. The diagnosis rests between a persistent omphalomesenteric duct and patent urachus. If a fecal fistula is present, the latter is more certainly excluded.

Tumors arising in the diverticulum cause indefinite primary symptoms referable to the tumor itself, and more pronounced secondary symptoms arising from superimposed complications. Lower abdominal distress and intermittent, moderately severe, cramplike pain have been found in 50 per cent of the cases. Frequently, the pain may be referred to the epigastrium. The tumor was palpable in 5 of the 20 cases reviewed by Nygaard and Walters.[1] Two of these were revealed by pelvic examination. Mention is made of the tendency for the tumor to slip away from the examining hand. Generally, symptoms and signs depend not so much on the size of the tumor as on the secondary complications, such as bleeding, intussusception, obstruction, perforation and local or diffuse peritonitis. In most of these patients, preoperative x-ray studies of the passage of barium through the small bowel have not been employed because of the signs of an acute inflammatory condition. Consequently, the literature on the positive roentgenologic findings has

been meager. In the less acute cases, however, serial studies of the small bowel — namely, films taken hourly for five hours after administration of the barium — may demonstrate the lesion. In 6 of the 22 cases of malignant disease reported to date, the diverticular lesion was demonstrated roentgenologically.

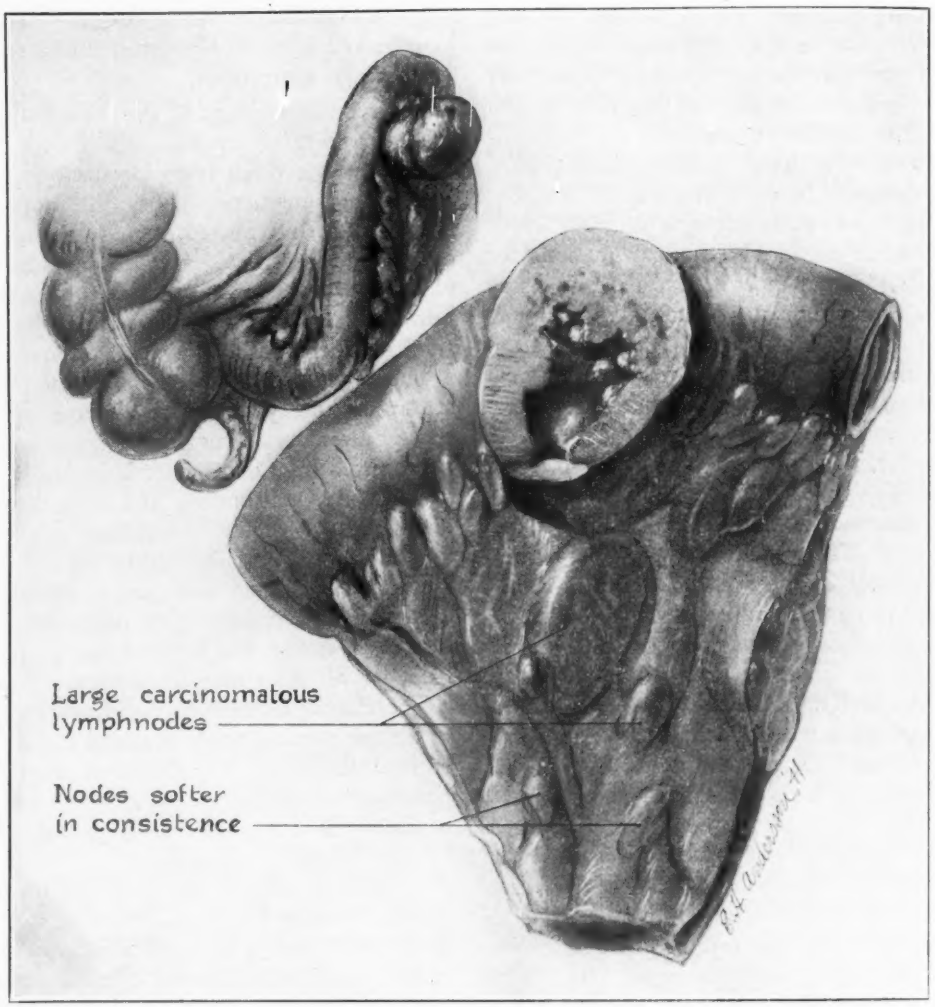

FIGURE 1.

CASE REPORT

Mrs. M. K., a 48-year-old Greek–American housewife, was admitted to the New England Baptist Hospital, under the care of Dr. Peter Comanduras, on November 24, 1940, with a chief complaint of abdominal pain of 3 days' duration. Except for intermittent abdominal discomfort for 17 years, for which she had had much medical care, the patient had been well.

For 3 days, there had been general abdominal pain of slight severity. This became worse 24 hours before admission and shifted to the lower abdomen, with tenderness and discomfort in both lower quadrants. There had been gradual development of slight distention and borborygmi, but no nausea, vomiting, constipation, diarrhea, fever or chills. The menstrual history was irrelevant. There had been no previous operations, and no significant loss of weight.

Examination revealed a well-preserved woman, who appeared moderately ill and complained of lower abdominal pain. The temperature was 99.8°F., the pulse 92, and the respirations were normal. The abdomen was moderately rounded and tympanitic, with definite but not marked distention. There were diffuse soreness and tenderness in both lower quadrants, without localized signs. Spasm was voluntary, and no mass was palpable. Manipulation of the uterus bimanually caused lower abdominal pain. However, there was no adnexal mass or tenderness, and there was no mass in the rectouterine pouch of Douglas.

The white-cell count was 9000, and urinalysis was normal. A diagnostic x-ray plate of the abdomen showed a moderate amount of air in the stomach and a lesser amount in the large bowel. There was no small-bowel distention. Gastrointestinal x-ray studies during the previous year had been reported as normal, and had not shown the presence of either a tumor or a Meckel's diverticulum. The clinical picture was regarded as atypical, and the tentative diagnosis of an acute surgical condition of the abdomen, probably acute appendicitis, was made.

Operation on the evening of admission by one of us (H. L. A.) was carried out through a right-lower-quadrant paramedian incision, with retraction of the rectus muscle laterally. A moderate amount of brown, turbid fluid without odor was encountered, culture of which produced no growth. Exploration revealed the viscera, including the large and the small bowel, to be normal except for the terminal ileum, 20 cm. from the cecum. On delivery of this portion of the bowel from the pelvis, there was a gush of yellowish exudate, resembling pus, but still without odor. At this part of the ileum, and arising 1 cm. from the mesenteric border, there was a firm, tensely filled, whitish, cylindrically-shaped 4-by-3-by-3-cm. mass, with markedly enlarged lymph nodes in the regional mesentery. The adjacent nodes were hard and grossly carcinomatous, whereas the more distant nodes at the root of the mesentery were soft and edematous in appearance.

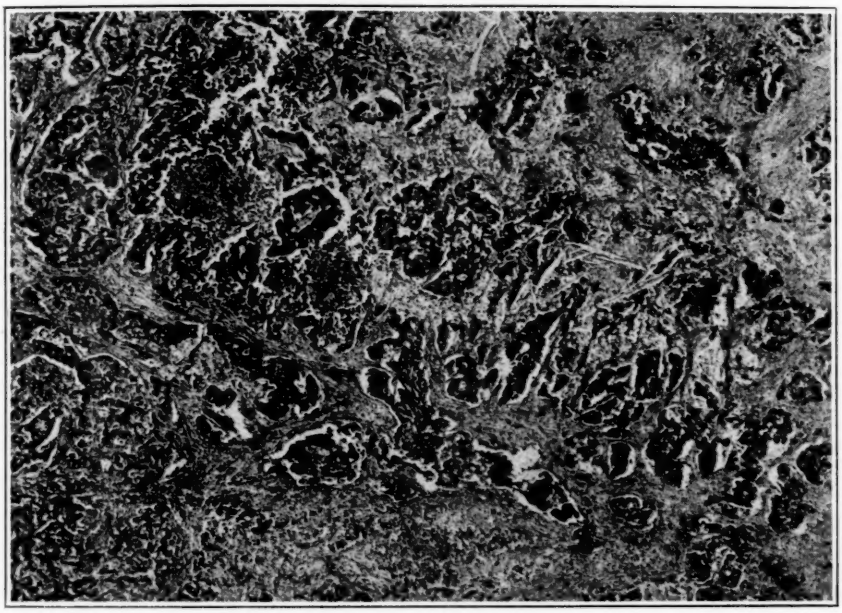

FIGURE 2.

Resection of 30 cm. (12 inches) of the ileum was carried out, including a margin of 10 cm. of ileum on each side of the lesion. A V-shaped portion of the corresponding mesentery and enlarged lymph nodes was included in the resection. End-to-end anastomosis of the ileum was done, with the use of the Furness clamp. Precautionary ileostomy was performed by inserting a No. 20 catheter in the ileum 15 cm. proximal to the anastomosis. The catheter was then brought out through the omentum and a separate small stab incision in the abdominal wall. The incision was closed without drainage.

The pathological report by Dr. Shields Warren was as follows:

> The specimen consists of a portion of ileum with adjacent mesentery, 30 cm. in length, which is essentially normal except for a firm and reddish mass, 3.5 cm. in diameter, extending into the mesentery (Fig. 1). The surface is smooth and rounded. Nearby, in the mesentery, is a firm, dull-gray mass measuring 3 by 2 by 2 cm., and a third mass 2 by 1 by 1 cm., which is somewhat soft and dark red. On opening of the bowel, the mucosa is entirely normal except for an opening 0.2 cm. in diameter. This communicates with a central lumen in the mass which projects into the mesentery. On section, this mass has a well-developed muscularis and a serosa, and is lined by mucosa continuous with mucosa of the bowel. From its base, an irregularly polypoid growth, covered with greenish exudate, protrudes into and practically fills the lumen. On section, this polypoid growth is 1 cm. thick, and shows gray, fibrous tissue, with scattered foci of necrosis extending out to the serosa, which at this point is yellowish gray. The remaining mucosa of the diverticulum is of normal thickness and communicates smoothly with the mucosa of the ileum. The larger mass in the mesentery, on cut section, is homogeneous and yellow gray. The smaller mass, on section, is reddish gray and hemorrhagic.
>
> On microscopic examination, the diverticulum is seen to have a well-developed muscularis; in the region of the tumor, this is heavily and irregularly infiltrated by masses of epithelial cells, which, in most places, form irregular glands (Fig. 2). Much of the inner aspect is completely necrotic and infiltrated by polymorphonuclear leukocytes and fibrin. Some of the tumor has penetrated the muscularis and is growing out into the mesentery. The cells of the tumor are irregularly but frequently cuboidal, or low columnar, and contain scattered mucous ductlets. The nuclei are oval and moderately vesicular, with usually a single prominent nucleolus. Mitoses are fairly frequent. In the diverticulum, there is no evidence of gastric mucosa.
>
> Sections of the mesenteric masses show similar tumor tissue, with varying degrees of necrosis.
>
> Diagnosis: adenocarcinoma arising from Meckel's diverticulum, with metastasis to two lymph nodes.

Convalescence was normal until the 11th day, when removal of the ileostomy tube was followed by brisk hemorrhage through the stab incision, which had been made

too close to the left inferior epigastric artery. The hemorrhage was controlled by a tight pressure dressing, however, without further intervention. The patient was discharged on the 21st postoperative day.

She has been seen periodically since then, the last visit being in June, 1941, 7 months after operation. A check-up gastrointestinal x-ray series, 3 months after operation, revealed a well-functioning anastomosis. At the last visit, the patient's general health was good, and there was no evidence of recurrence or metastasis.

This is the seventh case of carcinoma arising in a Meckel's diverticulum that we have been able to find reported in the literature. Most of these reports have been made in recent years. The previous 6 cases were reviewed by Nygaard and Walters[1] in 1937 (Table 1). Only 1 case, that reported by Gray and Kernohan,[7] showed the adenocarcinoma arising from gastric mucosa within the diverticulum.

TABLE 1. *Cases of Carcinoma Arising in Meckel's Diverticulum Reported in Literature from 1931–37.*

AUTHOR	AGE OF PATIENT	TYPE OF NEOPLASM	TREATMENT
	yr.		
Wiseley[8] (1931)	41	Medullary carcinoma	Removal
Copeland[9]	?	Adenocarcinoma (? of umbilicus)	Removal
Michael and Bell[10] (1932)	76	Adenocarcinoma	Removal
Franke[11] (1933)	54	Adenocarcinoma	Removal
Brown[12] (1933)	62	Medullary carcinoma	Removal
Gray and Kernohan[7] (1937)	37	Adenocarcinoma (arising from gastric mucosa)	Removal

In all 7 cases, removal of the diverticulum, tumor and regional metastatic areas was carried out, with reasonable expectancy of immediate salvage of these patients. Although more information regarding the late results in these patients would be helpful, it seems from this experience that the malignant tumor manifests no more rapid rate of growth than carcinoma of other portions of the intestinal tract. It also seems evident that the local complications usually produce symptoms early enough to allow timely radical resection of the growth before widespread dissemination occurs.

The need for generous resection of both intestine and mesentery well lateral to the growth is emphasized, to include any lateral lymphatic extension of the metastases around tumor-blocked lymph channels in the mesentery.

Reports of sarcoma arising within a Meckel's diverticulum have been more frequent, with 16 cases reported in the literature (Skinner and Walters[2]). Clinically, these sarcomas differ little from the carcinomas in that both give rise to symptoms when such complications ensue as ulceration, hemorrhage, obstruction by pressure or intussusception, and perforation. The sarcomas have usually been much larger primary tumors than the carcinomas, but most have been likewise resectable.

SUMMARY

Increasing clinical recognition of the many possible complications that may arise in a Meckel's diverticulum continues to stress the value of early control of these complications and even removal of the uncomplicated diverticulum whenever feasible. In the majority of cases, the complications are acute, and the diagnosis is uncertain or unsuspected. The responsibility therefore often lies heavily on the surgeon to recognize the lesion at operation, as in our patient. This may be difficult in the presence of marked obstruction, peritonitis or a large tumor, with or without metastases. Attention has been directed here to the occurrence of malignant neoplasms arising in a Meckel's diverticulum, more particularly to carcinoma, with the report of a case in which the growth was removed and an immediate successful outcome secured.

412 Beacon Street

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MEDICAL PROGRESS

GYNECOLOGY: ENDOMETRIOSIS

JOE V. MEIGS, M.D.*
BOSTON

IN this review, endometriosis and adenomyosis are considered two separate entities. Endometriosis is used to describe widespread areas of ectopic endometrium; an endometrioma is a single area of ectopic endometrium. Adenomyoma indicates the growth of tissue from the true endometrium into the myometrium, whereas adenomyosis indicates a diffuse involvement of the uterus. This is not an absolutely accurate division but, for the purposes of this review, will suffice. Adenomyosis is a fairly clear-cut entity with a satisfactory explanation, whereas great controversy still rages concerning endometriosis. Cullen[1] has shown that most uterine adenomyomas are due to the direct downward growth of endometrium into the myometrium, and direct connections were demonstrated in most of his cases. Adenomyoses or adenomyomas are often responsible for dysmenorrhea and abnormal bleeding, and are more frequently found in patients who have had many pregnancies rather than a few, in contrast to endometriosis. Adenomyosis is usually found in older women and is often reported from the laboratory when not suspected clinically. The treatment is, as a rule, removal of the uterus. Sometimes, adenomyomas are found as diffuse, fibroidlike areas in the uterus, but without capsules; they appear to be fibroids, but do not shell out of the myometrium as fibroids do. An adenomyoma is microscopically similar to an endometrioma.

Endometriosis is a very live topic principally because of Sampson's[2-4] epoch-making studies and, more recently, because of its apparent increase in frequency[5] — whether this is an actual increase or not, it is as yet impossible to state. Experimental work on the problem has been carried out and will be described later, but its true explanation is not yet established. Associated as it is with infrequent child bearing and sterility, it is of great importance to all. Endometriosis or endometriomas may be found in many areas, but nearly all are pelvic or close to the pelvis. The disease is rarely found outside the organs and peritoneum of the true pelvis, and yet there is no acceptable reason why it should not be. Endometriosis has been found in the arm, the lung, the leg, the round ligament in the inguinal canal, the vulva, the cervix and the perineum, and the explanation of these lesions has not been satisfactory. All the pelvic organs and parts of the pelvic peritoneum have been involved, some for one reason and some for others.

SYMPTOMS AND DIAGNOSIS

The symptoms of endometriosis are well known. They may or may not consist of a definite group, or any one of the usual symptoms may be present, or there may be none at all. Typically, the patient complains of painful menstruation or at least of menstrual pain, abnormal flowing, a change in the type of period or backache. Examination may be negative, or there may be masses in the broad ligaments or nodules in the uterosacral ligaments when the patient is examined by rectum. A hard beady or shotty feeling in the cul-de-sac on vaginal or, especially, rectal examination may suggest the correct diagnosis. There has been very little new progress in the evaluation of symptoms or physical examination. Special nodules, such as those occurring in the vulva, groin, umbilicus and abdominal scars, frequently swell before the menstrual period, and this swelling with a definite rhythm usually makes the diagnosis easy. Lesions in the rectovaginal septum may be seen as red, buttonlike areas or as a conglomeration of blue spots; the diagnosis is easy if considered. Endometriosis of the bowel is never difficult to diagnose, for bleeding may occur and is usually rhythmic. The tumor is often behind the mucous membrane, and the x-ray picture may show uninjured bowel mucosa. The presence of acquired dysmenorrhea or premenstrual pain and the occurrence of a mass are very significant, and at operation the finding of characteristic puckered areas with blue spots or the presence of pelvic endometriosis should clinch the diagnosis of endometriosis in the bowel.

TREATMENT

There has been no outstanding contribution to the treatment of endometriosis. For years, it has been known that removal of the ovaries or their destruction by means of radiation stops the growth

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. $4.00).

*Instructor in surgery, Harvard Medical School; chief of Gynecologic Service, Massachusetts General Hospital; gynecologist, Pondville Hospital.

of the tumors and allows atrophy to take place, as it does in the endometrium itself. The radical treatment is total hysterectomy, with bilateral salpingo-oophorectomy, and the conservative treatment is to excise the areas in the ovaries, peritoneum or other accessible places. If, after conservative treatment, recurrence takes place, radium or x-ray therapy will destroy the ovarian hormone output, and the lesions will atrophy. Excision of the small peritoneal lesions has long been carried out, and some observers have recently recommended the fine nasal cautery to destroy each of the small implantations found on the peritoneum. Since Cotte[6] advocated resection of the superior hypogastric plexus (presacral nerve) for dysmenorrhea, it has been obvious that this operation should be tried to check the pain of endometriosis; it has been advocated by many.[7, 8] Counseller[9] has lately changed his ideas and suggests its use only in cases of uterine adenomyosis, because from the knowledge of the areas affected by this nerve plexus it is unlikely that resection would stop the pain of endometriosis involving the broad ligament or other pelvic structures. Section of the nerve involves the uterus only, and therefore should relieve only uterine pain. Cooke[10, 11] has recognized this and carries out ovarian neurectomy to relieve ovarian pain by cutting the infundibular pelvic ligaments — the best way to section the sympathetic nerves of the ovary. If there is no damage to the ovary by interfering with the blood supply, it is much more reasonable to expect relief by this method than by resection of the presacral nerve.

The use of hormones to suppress menstruation completely by interfering with the pituitary gland should help, but such treatment cannot be carried on long enough to obtain any permanent result. Testosterone will suppress menstruation for months, but may cause growth of hair if too much is used, or if it is employed for too long a period. It is therefore not advocated. Estrin, which has been given to prevent ovulation[12] and thus prevent true or uterine dysmenorrhea, should prevent the pain of adenomyosis, but it should not affect the lateral masses of endometriosis that are responsible for flank pain. Sturgis[13] believes that the pain of endometriosis may be due to the premenstrual congestion that nearly always precedes menstruation and thus causes swelling of scarred and fibrotic endometrial lesions. Prevention of ovulation with estrin would not prevent edema, but testosterone, by inhibiting the pituitary gland and therefore all action on the ovary, will prevent edema and therefore eliminate painful swelling.

Treatment of endometriosis should therefore consist in conservative surgery, with the destruction or removal of small areas of ectopic endometrium in women desiring children, or radical surgery in the older age group — that is, by removal of all involved tissue, with the preservation of ovarian function, radiation being used if growth continues. It is well to caution the operator who attempts to do a total hysterectomy to remember that in these cases the posterior cul-de-sac and the rectum may be pulled up and frozen to the back of the uterus at the level of the internal os; an attempt to free this cul-de-sac to allow an approach to the cervix may result in a hole in the bowel. It is far wiser, if one is confronted with an extensive case of endometriosis with its tough adhesions, to remove all tumor and organs that can easily be removed, and trust to radiation later, than to perforate the bowel in an attempt to do a radical removal.

Results of Treatment

The results of radical treatment are excellent. The subsequent menopause can be treated satisfactorily by ovarian hormones, although this treatment may stimulate the growth of remaining endometrial tissue. Conservative treatment results in from 9 to 26 per cent of reoperations.[7, 14, 15] Inasmuch as most conservative operations are done for preservation of childbearing, it is essential to note that from 9 to 32 per cent of patients[14, 16, 17] become pregnant subsequent to operation. There is no doubt of the value of conservative procedures, but it should always be explained to the patient that there is a definite possibility of radiation or further surgery. The relief of pain following conservative surgery is great, but in some cases, early reoperation has been necessary, and in others, late. The endometriosis progresses slowly but steadily under the influence of the ovarian hormone, estrin.

Etiology

The greatest interest in this entity concerns the theories of its etiology, about which many controversies still rage. The main one concerns whether Sampson's theory of tubal reflux is correct or not.

Of first importance is the fact that endometriosis or adenomyosis is a comparatively newly recognized entity. In 1897, Cullen,[18] at a meeting of the Johns Hopkins Hospital Medical Society, reported his first case of adenomyoma of the uterus. In 1897, Pfannenstiel[19] reported the first case of adenomyoma of the rectovaginal septum. Russell[20] reported, in 1899, the finding of endometrial tissue in the ovary; he also removed a

small, pea-sized nodule of endometrial tissue from the right uterosacral ligament. In 1918, Cullen[1] operated on a patient with an adenomyoma of the rectovaginal septum and a widespread growth of the sigmoid. In 1909, Meyer[21] reported the history of a patient, operated on by Mackenrodt for adenomyoma of the bowel, who had had a resection done. In 1921, Sampson[2] reported his first group of patients with perforating hemorrhagic cysts of the ovary and demonstrated the presence of endometrial tissue in them and in the pelvic peritoneum. In 1922, Janney[22] reported a group of patients with endometrium in the ovary. From the time of Sampson's first report, the literature has teemed with articles on endometriosis, a partial list of which is appended at the end of this review. Sampson has written by far the most numerous and most carefully prepared papers and has given not one but numerous theories of its development. However, the one that is usually regarded as his greatest contribution concerns the question whether or not endometrium can flow through the tubes during menstruation and become implanted on the ovary and peritoneum of the pelvis. Since Sampson's great paper, many other ideas of the etiology have been presented.

The theory of von Recklinghausen that adenomyosis and endometriosis are due to growth of left-over pieces of the Wolffian ducts has long been discarded. It is far likelier that these conditions arise from cell remnants following the formation of the Muellerian ducts. This will be discussed later. Iwanoff[23, 24] and Meyer[25] independently advocated the idea that the epithelium of the pelvis, inasmuch as it is the celomic epithelium from which the Muellerian ducts arise, can under certain circumstances, such as irritation due to inflammation or injury by menstrual blood, undergo metaplasia and produce Muellerian epithelium or endometrium. This theory is plausible and has many advocates. It explains most endometriosis satisfactorily. Heim[26] supports this theory by stating that endometriosis occurs only in tissue that is derived from the original celom. He believes that it may be derived from the mesothelium, endothelium or germinal epithelium of the early embryonic celomic cavity. Bell[27] and Robinson[28] actively join the theory of Iwanoff and Meyer, both believing that the celomic epithelium under certain circumstances may be the source of the ectopic endometrium.

Halban,[29, 30] in 1924, advanced the idea that pieces of tissue metastasized by way of the lymphatics, and suggested that the sites of endometriosis were best explained by lymphatic routes. It is true that this theory best explains the presence of endometrial glands in lymph nodes of the pelvis. In operations for cancer of the cervix, such lymph nodes have been found and described. Taussig[31] has recently found such nodes in cases in which he has done pelvic lymph-node dissections following radiation treatment of cancer of the cervix. This method of extension of endometriosis may best explain the report of Büngeler and Fleury-Silveira[32] of endometriosis in the pleural cavity; however, extension to the chest cavity may also be explained by metastasis through the blood stream.

Sampson's various theories, some not generally known, are as follows:

During menstruation, pieces of tissue are cast off, and some of this tissue may flow in retrograde method through the tube and, being spilled out, may grow on the ovary or the peritoneum, where such particles may alight.

Pieces of endometrium may grow into the wall of the fallopian tube, or may be caught in the fimbrias of the tube and grow there.

The tubal mucosa itself may act in response to the ovarian hormones and may occasionally menstruate, and pieces of tubal epithelium may be implanted by contiguity on the ovary or any other structure it may touch.

An ovarian endometrial blood cyst may rupture and spill pieces of endometrium into the pelvis that may grow — Sampson agrees that there is no positive proof of this.

An endometrioma of the ovary may become attached to a pelvic structure, and because of the adherence to the peritoneum, areas of endometrium may grow into the contiguous peritoneum.

Cast-off endometrium may go so far as to implant itself in a hernial sac and thus may account for endometriosis in the groin found in a hernial sac.

It can also spread by way of the lymphatics and blood vessels, and thus find its way into the round ligaments.

There are many reasons for Sampson to believe in his major theory, for he has seen what he considers viable endometrial tissue surrounded by blood in the material flowing through the tubes at laparotomy. The lesions of the ovary are on the lateral and under surfaces, an especially good place for blood to strike the ovary as it comes out of the tube. He believes that peritoneal implants are so small that they do not participate so perfectly in menstruation as ovarian endometrial cysts. He also believes that, if the bits of endometrium carried into the pelvis through the tubes are dead, his theory is dead. His theory has support from the work of Bartelmez,[33] who on examining uteri removed and fixed immediately after laparotomy says that even the tissue fragments and cell masses free in the lumen on the first day of the menstrual flow have many cells that appear normal histologically. Such support is very satisfactory. However, the work of Markee[34] is extremely damaging to Sampson's theory. Markee transplanted living endometrium of the uterus of the monkey into the eyes of the same monkey and obtained a

very large percentage of takes. By this method, he was able to view menstrual cycle after cycle either by the naked eye or by microscope. He makes the following observation: "Although thousands of fragments were observed in the 432 menstrual periods studied since 1928, not a single reimplantation of a fragment was noticed. It was seen that the fragments settled to the bottom of the anterior chamber [of the eye] and disintegrated. Occasionally one would remain whole for 36 hours but most of them disappeared within one hour and many within 30 minutes." This suggests that, in the monkey, endometriosis cannot be due to the implantation of such fragments, which are not viable, at least not in the anterior chamber of the eye, although Cron and Gey[35] reported a growth of desquamated fragments in tissue culture. The work of Cron and Gey, to which a great deal of weight has been given in the past in support of Sampson's theory, is of questionable value, for the tissue that was grown on a plasmatic medium consisted of pieces of tissue obtained from a woman on the second day of the menstrual cycle that were removed by a *dull curette*. Leukocytes and connective cells and sheetlike outgrowths of epithelial cells were grown. The tissue was transplanted every four or five days for a month, but no increase in the mass of tissue occurred. In a footnote on the same paper, the authors state: ". . . additional experiments show that the fragments of epithelium [decidua menstrualis] normally found in the menstrual flow and obtained without the use of a dull curette, are visible. In general, as far as we have been able to determine, the decidua menstrualis, is more active when cultured in vitro than normal endometrium." No further reports have been found in the literature concerning the results of these later tissue cultures to enlarge on the footnote, and it is obvious, in view of Markee's work in the monkey, that this should be done, for proof is not present in the reported experiment.

In answer to the problem raised by Markee's work, many would say that the tissue of the eye is not similar to that of the pelvis, and yet it was possible to transplant endometrium into the eye easily. The work of Jacobson[36] demonstrates that the endometrium of the rabbit and the monkey will grow in the pelvis of those animals, more especially if the peritoneum of the pelvis is irritated or if the tumor is transplanted into the pelvic peritoneum. But such tissue will *not* grow in the remainder of the peritoneal cavity. Moreover, Jacobson found in some of his experiments that endometrium would grow after the ovaries were removed. However, the endometrium used was a transplantation, such as a skin graft and not an implantation as one understands Sampson's theory, and it is difficult to explain how implantation could occur in the human being unless some irritation of the peritoneum had occurred. The tissue used by Jacobson in his work was viable endometrium and not cast-off menstrual tissue. His difficulty with such material, and his ability to grow it only in the pelvis and Markee's difficulty with the eye make one think that perhaps the pelvic epithelium has some special value as a grower of endometrium or that it has in itself the inherent power to growth, and that the areas of endometriosis are responses to injury, as suggested by the Iwanoff and Meyer theory, rather than true implantations. It is obvious that more investigation must be done along the lines of Cron and Gey and of Jacobson before Sampson's theory of the growth of cast-off endometrium can be accepted. In about half the cases, the small peritoneal implantation functions as the endometrium does; in the other half, the endometrioma resembles the basal layer of the endometrium, which does not function. If Sampson's theory is correct, it seems that, since the endometrium cast off by the uterus must have been from the functional layer (compact layer), its implantation in the pelvic peritoneum should function and should not appear and act like the basal layer. Perhaps the cast-off functional tissue becomes the nonfunctional basal type. It seems, however, as if this suggested that the two tissues, cast off endometrium and implant, are not the same.*

There are three other recent reports of interest in the consideration of ectopic endometrium. Büngeler and Fleury-Silveira[32] report the presence of endometriosis in the pleural cavity, Navratil and Kramer[37] of endometriosis in the extensor carpi radialis muscle of the forearm, and Mankin[38] of endometriosis in the left thigh. The explanation of the chest-cavity extension, as noted above, is probably by extension through the lymphatics or veins of the vascular system, but that of the thigh and arm cannot be explained on any other basis than extension by vein. Hobbs and Bortnick[39, 40] have shown that viable endometrium can be transplanted to the lungs by way of the veins and that it will grow in the lungs. This is experimental proof that venous metastasis is a possibility. Until the excellent work of Batson,[41] it has always been impossible to explain the extension of tumors from the pelvis to bones and certain organs except through the lung, which presupposes the growth of a metastasis in the lung and subsequent extension to the left heart, or the

*On the other hand, Sturgis[42] believes that function depends on blood supply and hence a satisfactory supply of estrin, and that the functional endometrium that implants itself in the pelvis may be nonfunctional if the blood supply is not sufficient.

presence of an open foramen ovale in the heart. Too many unexplained metastases occurred, and the work of Batson, who has demonstrated a vertebral venous system, has unraveled the difficulties. This system of veins leads directly from the pelvic organs to the bones or, by connecting veins, to the veins of the extremities, without going through the caval system. In this way, the lungs can be detoured, and an endometrioma in the leg and arm and possibly one in the pleural cavity can be explained. These cases and Batson's work are in support of those who believe in the venous metastatic theory of endometrial extension. If the cases with endometrioma in the leg and arm are authentic, and it seems as if they are, the possibility of venous metastasis is a very significant theory of endometriosis.

It has always been difficult to explain why the small endometriomas seen in the pelvis are, when not accompanied by ovarian endometriosis, usually in the midline. Certainly, the uterosacral ligaments are difficult places for cast-off endometrium to light on and grow, as is also the area at the reflexion of the bladder flap on the uterus. Yet these areas are frequently affected. Such cases are better explained by the development of embryonal rests in the celomic epithelium or by venous or lymphatic metastasis. If endometriosis is due to the reflux of endometrium in menstrual fluid, the absence of tumors on the anterior abdominal wall and among the intestines and in the mesentery is hard to explain. Although the pelvis is the likely place for endometrium to rest when a woman is upright, it is not the dependent area in a woman lying on her stomach. A woman is quiet when sleeping, she menstruates when asleep, and at that time a reflux would be likelier, and implantation should occur more easily. Because endometriosis is not found in ventral areas and is nearly always in the pelvis, it is probable that the pelvic epithelium or celom has some special predilection for this lesion.

It was recently shown[5, 42] that there is a much greater percentage of endometriosis in private practice among well-to-do patients than in the wards of the Massachusetts General Hospital. It was suggested that the reason for this was earlier marriage and earlier childbearing in the hospital group than in the private group. It was thought that birth control and spacing of children were having a serious effect on the fertility of well-to-do young women. Lack of early marriage and childbearing in young women is serious, for endometriosis is often accompanied by infertility. Monkeys in the jungle mate as soon as they become of age and have offspring until they either physiologically cannot have any more or die, but some women go at least twelve years without interruption of their menstrual periods. This is not normal. Twenty-eight per cent of 400 private patients had histologic endometriosis, in contrast to only 5 per cent of the ward patients at the Massachusetts General Hospital (Table 1). Only 66 per cent of married women with endometriosis in private practice were fertile, whereas 94 per cent of the hospital patients were fertile (Table 2). Seventy-three per cent of the private and 42 per cent of the hospital patients had two or less children; 53 per cent of private and 12 per cent of hospital patients were twenty-five years of age or over when married. Sixty-five per cent of the private patients, and only 40 per cent of the hospital patients, who had endometriosis had menstruated over ten years before the first pregnancy. All in all, there is a great difference between these two groups, and the great amount of endometriosis in the private group can be explained on the basis of delay of childbearing. These facts are evidence that menstruation during many years without interruption is the cause of endometriosis, and that it is due to the stimulation to growth of the celomic epithelium and its embryonal rests.

Another striking fact is that underdevelopment of the genital organs is a frequent accompaniment of endometriosis. Patients with congenital erosion of the cervix, severe dysmenorrhea and

TABLE 1. *Incidence of Endometriosis.*

TYPE OF CASE	CONSECUTIVE ABDOMINAL GYNECOLOGIC OPERATIONS	ENDOMETRIOSIS MICROSCOPICALLY		ENDOMETRIOSIS GROSSLY		ENDOMETRIOSIS MICROSCOPICALLY OR GROSSLY	
	NO. OF CASES	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
All cases							
Massachusetts General Hospital	400	21	5	11	3	32	8
Private	400	112	28	32	8	144	36
Excluding cases past the menopause							
Massachusetts General Hospital	344	15	4	10	3	25	7
Private	357	108	30	31	9	139	39

juvenile organs are very apt to develop endometriosis earlier than those without such stigmas. This suggests that if the uterus and the cervix are underdeveloped, so also may be the pelvic peritoneum; such patients are thus likelier to harbor embryonal rests and therefore more frequently have endometriosis. Late childbearing may allow more years of reflux bleeding, but the problem is more fundamental than that, and avoidance of normal function seems to be the cause. The pelvic or celomic epithelium, which is the only region that grows endometriosis, is probably stimulated to growth by abnormal physiologic function. It is therefore time to advocate the obvious — namely, that all women should marry early and bear children early.

TABLE 2. *Data on Patients with and without Endometriosis.*

STATUS	PATIENTS WITH ENDOMETRIOSIS		PATIENTS WITHOUT ENDOMETRIOSIS	
	PRIVATE	M. G. H.	PRIVATE	M. G. H.
	%	%	%	%
Married	74	86	74	82
Fertile	66	94	83	85
Two or less children	73	43	49	50
At marriage, 25 years old or over	53	13	39	18
At first pregnancy, 25 years old or over	63	18	—	—
From marriage to first pregnancy, 2 years or more	69	—	67	—
From menarche to first pregnancy, 10 years or more	66	56	40	28
From menarche to endometriosis, 17 years or more	83	65	—	—
At onset of symptoms, 27 years old or over	96	60	—	—
Stigma of underdevelopment	28	—	15	—

* * *

Many questions concerning endometriosis are still to be answered. For example, why do areas of ectopic endometrium menstruate when Bartelmez and Markee and others have shown that menstruation is such a complicated process, necessitating coiled arteries of a special type and the varied layers of the endometrium? Why does pain occur when the uterus is not involved? Why is it that small endometriomas in the peritoneum do not become large chocolate cysts? Why is endometriosis localized in the pelvis in nearly all cases? Can cast-off endometrium grow?

In recent years, the work of Batson demonstrating a vertebral venous system has been outstanding because it explains, by a detour around the lungs, the method of extension of malignant lesions as well as of endometriosis. The work of Markee and Bartelmez aids in the conception of menstruation and leaves a great deal of explaining to account for the action of ectopic endometrium. The work of Hobbs and Bortnick, by showing the viability of endometrium after venous extension to the lungs, is of great value. Cron and Gey's work should be repeated in a larger series of cases, for their experiments do not seem to be proved. The fact that ectopic endometrium has been found in the pleural cavity, the arm and the leg suggests that the theory of the venous pathway for extension of endometrium may be correct. Finally, the great frequency of endometriosis in private practice as distinguished from hospital-ward cases makes the questions of late marriage and late childbearing of great significance.

Progress has been made in the understanding of these lesions, but a great deal of work remains to be done.

264 Beacon Street

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28041

PRESENTATION OF CASE

First admission. A thirty-three-year-old Lithuanian-American housewife entered the hospital because of increasing dyspnea.

She had been quite well until a year and a half before admission, when dyspnea on exertion developed insidiously, accompanied by a vague feeling of substernal oppression. Six months before entry, slight cyanosis began to accompany the episodes of dyspnea. The patient began to sleep with an extra pillow, and experienced occasional nocturia. Six weeks before she entered the hospital, a physician gave her "heart pills," which she took for two weeks, without improvement in her condition. She then noted for the first time that her legs and abdomen were swollen, and that she had gained 30 pounds in weight. Additional pills "for the edema" were given by the physician, without noticeable effect.

Prior to the onset of her illness, the patient had often taken long walks without difficulty. She had had "pleurisy" thirteen years before. She denied syphilitic or rheumatic disease and had never been told of any cyanosis or functional disability in infancy. Two siblings had died in infancy of unknown causes, and her father had died at fifty-four of a "heart attack." She had been married for thirteen years but had never been pregnant.

Examination showed an obese, plethoric, quite cyanotic woman in moderate respiratory distress. The heart was enlarged, especially toward the left, with a diffuse apical impulse. The rhythm was regular. The heart sounds were distant, with accentuation of the pulmonic second sound. There was a systolic murmur, best heard at the left border of the sternum. The lungs were normal. The abdomen was distended, and slight shifting dullness was present in the flanks. The liver and spleen could not be felt. There was pitting edema of the lower extremities, and of the abdominal wall below the waistline. There was questionable distention of the veins of the neck. The fingers showed no clubbing.

The temperature was 98°F., the pulse 100, and the respirations 35. The blood pressure was 140 systolic, 110 diastolic.

Examination of the blood showed a red-cell count of 5,200,000 with 19 gm. hemoglobin, and a white-cell count of 8880 with 73 per cent polymorphonuclears. Oxygen studies of arterial whole blood showed 93 per cent saturation; the carbon dioxide combining power of the plasma was 70.7 vol. per cent. The cell volume was 51.3 per cent. The urine showed ++ to +++ tests for albumin on eleven out of twelve examinations. Only occasional red or white cells appeared in the urinary sediment.

In a roentgenogram of the chest, the heart appeared enlarged, without any characteristic configuration. The left main bronchus seemed slightly elevated. There was fluid in both pleural cavities.

The electrocardiogram demonstrated right-axis deviation. In Lead 1, the QRS complex was slurred, and the T wave was flat. In Leads 2 and 3, the T wave was inverted, with sagging of the ST segment. The PR interval was 0.19 second.

The patient was treated with bed rest, and with restriction of fluid and salt intake. Rapid digitalization was accomplished, and Mercupurin was given intravenously every few days. An oxygen mask was used almost constantly at first, with marked improvement in the cyanosis. The diet was restricted to 800 calories daily, with added thiamin chloride, nicotinic acid and cevitamic acid. There was satisfactory diuresis, the weight dropping from 220 to 165 pounds in the course of a month's stay in the hospital.

Final admission (three months later). After the patient's discharge from the hospital, she was followed in the Out Patient Department. The dietary restrictions were maintained, and the patient continued on digitalis. She felt improved for the next two months, after which she was again troubled by cyanosis and dyspnea on exertion. The next week, she remained in bed, taking ammonium chloride. She slept poorly because of orthopnea. Because of increasing breathlessness, she re-entered the hospital.

Examination showed extension of the area of cardiac dullness, which was 15 cm. to the left of the midline at the apex, and 8 cm. at the level of the third interspace. A blowing murmur at the third left interspace filled all of systole. A rushing diastolic murmur was audible at the apex when the patient was placed in the upright position. The pulmonic second sound was split, and louder than the corresponding aortic sound. The border of the liver lay three fingerbreadths below the costal margin. The legs were cold, and

pitting edema extended as far as the chest.

The blood pressure, temperature, pulse and respirations were approximately as before.

During the night, although the patient was kept in an oxygen tent, she remained cyanotic. Early the next morning, she suddenly began to gasp and died within a few minutes.

Differential Diagnosis

Dr. T. Duckett Jones: I wondered briefly if the increasing dyspnea in episodes could have been due to asthma. However, the patient had been examined within a reasonable period of the onset of her illness, and nothing had been found.

The dyspnea on exertion and the vague feeling of substernal oppression were, I presume, early symptoms of left-sided failure.

Cyanosis then assumed a greater part in the picture. The only feature that seems to be left out of the ordinary development of left-sided failure is cough, which the patient apparently did not have.

The swollen legs and abdomen and the increase in weight indicate further progression of heart failure.

"Prior to the onset of her illness, the patient had often taken long walks without difficulty." I suppose that this indicates that she was actually well up to thirty-one and a half years of age, or eighteen months before the onset of symptoms.

She had pleurisy thirteen years before admission. The history of pleurisy with pain does not help determine what the actual diagnosis was at the time.

Apparently, congenital heart disease was thought of because of the findings that later developed, and the note concerning well-being in infancy was put in to indicate that there was no evidence early in life of congenital heart disease.

"Examination showed an obese, plethoric, quite cyanotic woman in moderate respiratory distress." There seems to have been more cyanosis than is routinely seen in ordinary heart failure.

"The rhythm was regular." That is very important.

There was a loud pulmonic second sound, at the age of thirty-three. That probably represented some increased pulmonary pressure.

The systolic murmur at this stage means nothing to me; it is not at all unusual in various types of heart disease and in normal hearts. The murmurs described throughout are confusing. Gouley[1] has pointed out that basal systolic murmurs may have some role in pulmonary disease, which certainly comes in as one of the features of differential diagnosis later on in this case.

So far, everything fits congestive heart failure quite well. Why the liver was not felt, I do not know. The ascites apparently was not tremendous, so that one would believe that the liver was not palpable.

"The fingers showed no clubbing." Congenital heart disease in adult life is usually associated with clubbing of the fingers.

I suppose the elevated diastolic pressure might go along with peripheral failure, which the patient obviously had.

The carbon dioxide combining power of the plasma was about 10 vol. per cent above normal, which is probably consistent with congestive failure. There was a distinct increase in the cell volume, indicative of hemoconcentration.

In the absence of further reports of urinary sediments and since no blood chemical findings were reported, I presume that the renal picture was the result of congestive heart failure, rather than primary renal disease.

Obviously, there was right-sided and left-sided enlargement of the heart by roentgenogram. The slightly elevated left main bronchus makes one think of a large left auricle, which is frequently associated with mitral stenosis. Both pleural cavities had some degree of fluid, although the amount is not stated.

The electrocardiogram demonstrated right-axis deviation. I take it from the original description of this patient that she was not of the stature that would normally have right-axis deviation of the heart. She was apparently an obese, short, stocky person, and might conceivably exhibit left-axis rather than right-axis deviation. Thus, the finding is significant and indicative of right-sided heart damage, of either a temporary or a permanent character.

The inverted T wave and the sagging ST segment suggest that the patient received digitalis shortly before entry into the hospital.

In view of the fact that the majority of patients with congestive failure do not require oxygen therapy, I should assume that the cyanosis was out of proportion to the ordinary features of failure observed in this case.

The restricted diet was probably prescribed on the basis of obesity — to decrease the patient's weight, as well as to get rid of edema fluid by other methods. There is no evidence that the heart status was due to the so-called "beriberi heart."

The patient must have been broad chested to have a 15-cm. left border. The left heart border was obviously well in the axilla, probably with some auricular and left ventricular enlargement.

The murmur of mitral stenosis is not often described as a rushing murmur. I do not know whether the rushing murmur was high or low pitched. I know that the murmur of mitral stenosis is heard better with the patient recumbent in the left lateral position than with the patient erect. I know that a blowing diastolic murmur, from aortic regurgitation, or possibly a basal diastolic blowing murmur, which may be called or considered a Graham-Steele murmur, is heard best in the erect position. Hence, the description of the murmur confuses me considerably. However, one can state that there was a change or progression in the decreased function of the heart in this case.

"The pulmonic second sound was split, and louder than the corresponding aortic sound," again indicative of an increase in pulmonary pressure.

"The border of the liver lay three fingerbreadths below the costal margin." This, together with the extensive peripheral edema, certainly indicates right-sided failure.

This picture is distinctly confusing. There is no history of preceding congenital defects, and many types of heart disease that one thinks of do not fit the picture very clearly. We can comparatively easily rule out the nephritic possibilities; the patient did not have hypertension at the end, and there is no evidence of uremia. The ordinary hypertensive syndrome, with a progressive course over a period of less than two years, would probably have exhibited hypertension at the end, and it is likely that the breaks in compensation would have been more acute and accompanied by more sudden episodes of left-sided failure and generalized symptomatology before the patient would have been bedridden. In addition, she had enlargement of both sides of the heart by x-ray and by physical examination, as well as right-axis deviation, which indicates that there was some right-sided dilatation.

Coronary disease, I think, we can reasonably dismiss. There was no acute episode. This does not always occur, but the patient did not have a low blood pressure at any time. There was never any severe pain, and the electrocardiographic picture is not characteristic of coronary disease.

Cor pulmonale, either acute or chronic, must be thought of. Acute cor pulmonale can be ruled out because there was no severe acute episode indicative of extensive infarction or thrombosis. The patient had no shock, no severe pain and no hemoptysis and she did not have the typical electrocardiogram of an acute cor pulmonale. So far as chronic cor pulmonale is concerned, the possibility of Ayerza's disease, which the cyanosis suggests, can be ruled out on the fact that she did not have so long a period of decreasing pulmonary reserve as is observed in most cases of pulmonary fibrosis. The feature most in favor of cor pulmonale of more chronic form is the right-axis deviation.

Certainly, this is not the picture of syphilitic heart disease.

That leaves a large group of cases of heart disease — the rheumatic. In addition, there remain other types, such as unusual tumors, which I am not qualified to discuss. So far as rheumatic fever is concerned, the patient was fairly young and had had no previous rheumatic history. In rheumatic heart disease discovered for the first time in adult life, mitral stenosis is usually present; it is almost the characteristic feature of slowly or insidiously developing rheumatic heart disease, and is often accompanied by relatively little cardiac hypertrophy. The patients with mitral stenosis who have failure in middle life usually develop auricular fibrillation. In rheumatic heart disease with mitral stenosis for years, with hypertrophy probably as the result of myocardial change of previous attacks of rheumatic fever, there are often embolic phenomena, of which there is no evidence in this case. No murmur of mitral stenosis was heard when the heart rate was 100, and there was no failure. Save for one possibility, I believe we can discard the possibility that mitral stenosis was present. A large left auricle, as suggested by x-ray examination in view of the elevation of the left main bronchus, if practically occluded by thrombus, might occur along with mitral stenosis, even in the absence of the typical murmur. I think this is a possibility, although a remote one. So far as the symptoms of straight rheumatic heart disease and the usual picture of rheumatic fever are concerned, I think they do not exist. Young children or young adults with rheumatic infection who die as a result of acute carditis practically always exhibit right-sided heart failure first and progress to left-sided failure. Evidence of the former develops in the absence of pulmonary symptoms. Such patients do not have dyspnea, and lie flat in bed. The patient under discussion did not exhibit this picture. She had symptoms of left-sided or pulmonary difficulty, in addition to obvious cardiac hypertrophy. Parker and Weiss,[2] in 1936, reported a case of mitral stenosis with pulmonary hypertension, and pulmonary-artery sclerosis, with extensive changes throughout the larger and smaller vessels and arteriolar system of the lung. They considered the changes that they described to be comparable to changes seen in the systemic arterioles in malignant hypertension and

to be capable of developing very quickly in two months. Evidence was presented, aside from the one case given in detail, of the fact that in mitral stenosis there are often changes in lung tissue. Gouley,[1] who has written extensively of the alterations in the lung in rheumatic fever, points out that the pulmonary-artery changes are not necessarily constant and dependent on the presence of mitral stenosis. They may be the result of a coincidental vessel and parenchymal change during active rheumatic fever. Gouley describes at great length the rubberoid lungs of chronic rheumatic fever, consisting of a parenchymal thickening and elastic-tissue weakening and hyperplasia. He also describes acute pulmonary consolidation, — so-called "rheumatic pneumonia or pneumonitis," — which this patient did not have at any time. An acute pulmonary rheumatic process is not essential for such vascular changes to be found at autopsy. In autopsies of rheumatic-fever patients, we have seen practically all the lesions Gouley has described. We have never been entirely convinced that pulmonary changes in rheumatic fever are usually the primary reason for failure in adult life. Except for episodes of acute left-sided failure in adult mitral stenosis, I believe that the valve lesion itself in rheumatic heart disease usually has little to do with failure, but in this case we have a patient with no known rheumatic fever who was ill for less than two years, and who had both right-sided and left-sided failure. If this patient had been fifteen, sixteen or seventeen, it would not have disturbed me too much, despite the fact that there was no clinical evidence of active rheumatic fever — joint pains and so forth. To my mind, there is one syndrome, with changes probably in the heart itself and in the lung, that can produce this picture — namely, a very low-grade rheumatic process. Aschoff bodies may not be found, since the process in the myocardium is a very chronic one and the pulmonary picture is apparently more important than the myocardial. This patient may represent the unusual case in which chronic rheumatic-fever pulmonary changes are of primary significance. My clinical impression is that rheumatic fever could account for this picture, and as a second bet I should say that some unusual type of congenital anomaly might explain the picture.

Dr. George W. Holmes: One or two things brought out in the films are not mentioned particularly in the notes, and I think they will help Dr. Jones a little. The extreme narrowing of the supracardiac shadow is very much in favor of his interpretation. I cannot imagine a supracardiac shadow so small as that in the presence of hypertension of any extent. In some of the films, there is evidence of either thickened pleura or fluid, as mentioned in the notes. Nothing was said about this change in the lung itself. I assume that this was attributed to fluid in the pleural space behind the area we are speaking of; however, it does not look like fluid, and one wonders if there was, at some time, some injury to that lobe, such as an infarct. The striking thing about the heart is the dilatation of the auricles.

Dr. Tracy B. Mallory: Does anyone want to hazard another diagnosis?

Dr. Wyman Richardson: I want to hazard one. I think Dr. Jones mentioned it and excluded it, but I wonder whether pulmonary arterial obstruction, possibly on the basis of pulmonary thrombosis, in a patient of this age should not be seriously considered as more likely than rheumatic fever.

Dr. Jones: You mean blocking the large vessels?

Dr. Richardson: An extending thrombosis.

Dr. Mallory: Dr. Bland, you saw this patient. Should you like to comment?

Dr. Edward F. Bland: About once a year, Dr. Mallory presents a very puzzling case of this nature. Several of us had followed this patient's course in the Cardiac Clinic, and she died on the medical ward when I was on service.

There are two important points in the history, whose sequence, I think, needs emphasis: the patient was breathless for a full year before she began to be cyanotic; thereafter, the cyanosis slowly progressed and at the end was extreme. Most of us considered seriously only two diagnostic possibilities: either some unusual congenital anomaly or primary disease of the pulmonary arteries. The clinical course was distinctly against the first and strongly suggested the latter. For the sake of the record, it should be stated that the arterial blood studies on this patient were done after she had been in an oxygen tent, and this alters the results considerably. Throughout her course, the physical signs suggested severe pulmonary hypertension, for which we could find no obvious explanation; we therefore concluded that this was obliterative pulmonary arterial disease and chronic cor pulmonale.

Clinical Diagnoses

Cor pulmonale.
Pulmonary endarteritis.

Dr. Jones's Diagnosis

Rheumatic fever, with extensive pulmonary changes, or
Possibly, congenital heart disease.

Anatomical Diagnoses

Cor pulmonale.
Hypertrophy and endarteritis of pulmonary arterioles.
Infarcts of the lung, small.
Pulmonary congestion, extreme.
Chronic passive congestion.
Peripheral edema.

Pathological Discussion

Dr. Mallory: It is very easy to cite the anatomic facts, but much more difficult to interpret them. This patient was found to have marked cor pulmonale; the right ventricle was from two to three times the normal size, and despite the marked dilatation, its wall measured 10 mm. in thickness against the normal of 4 mm. The pulmonary conus was distinctly dilated, although the main pulmonary artery was not. The branches within the lung, however, certainly were, and plaques of atheroma were very numerous. When we cut across the lungs, all the small vessels stood out prominently, had obviously thickened walls, and remained patent rather than collapsing as pulmonary arterioles ordinarily do. The lungs were heavy, and considerable amounts of fluid could be expressed from them. The mitral and aortic valves were absolutely normal. There was a slight question of minimal scarring of the tricuspid valve, but it was of normal diameter.

Microscopic examination of the heart showed nothing that would suggest acute rheumatic heart disease. On the other hand, microscopic examination showed the characteristic lungs of mitral stenosis. The alveolar walls were extremely thick and extremely edematous, and all the alveoli were filled with heart-failure cells. The pulmonary arteries were markedly hypertrophied; a few of them were thrombosed, but only a very few. I do not believe that one could claim on a quantitative basis that there were enough thrombosed pulmonary arteries to account for the right ventricular hypertrophy, and the type of change in the pulmonary arteries is much more what I should think was secondary to pulmonary hypertension than an obliterative endarteritis that might be the primary cause of a pulmonary hypertension. The mechanism by which all this is produced is completely beyond me.

Dr. Holmes: Was there anything in the right lower lobe?

Dr. Mallory: A small infarct.

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CASE 28042

Presentation of Case

A twenty-one-year-old Italian-American truck driver entered the hospital complaining of shortness of breath.

He had been well until six months before entry, when he began to tire easily. He felt weak, became dyspneic on slight exertion, and therefore quit work. Three months later, he was troubled with swelling of the face, ankles, penis and scrotum, which progressed until he experienced difficulty in urinating. Because of this, he consulted a physician, who gave him a course of thyroid, with resultant loss of about 10 pounds in weight. The swelling, however, persisted.

Two months before entry here, the patient was admitted to another hospital. His heart was found to be enlarged, extending 11 cm. to the left of the midsternal line in the fifth interspace. The rhythm was regular, with a rate of 51; the sounds were clear. The blood pressure was 112 systolic, 86 diastolic. Extension of the liver edge two or three fingerbreadths below the costal margin seemed likely, but could not be established with certainty, because of the obesity of the patient.

The blood showed a red-cell count of 5,400,000 with 109 per cent hemoglobin, and a white-cell count of 13,300 with 74 per cent mature polymorphonuclears. The blood Wassermann reaction was negative. The blood levels of cholesterol, sugar, nonprotein nitrogen and creatinine and the albumin-globulin ratio were within normal limits. The urine had a low specific gravity, and contained a slight trace of albumin, and occasional red and white cells and casts. Congo-red and phenolsulfonphthalein excretion tests were negative. The basal metabolic rate was –19 per cent.

A roentgenogram of the chest showed enlargement of the heart involving predominantly the left auricle and ventricle, and an apparent interlobar effusion between the middle and upper lobes of the right lung. A roentgenogram of the skull showed a normal sella. An intravenous pyelogram was negative. An electrocardiogram showed complete heart block, with abnormal ventricular complexes, including marked inversion of the T waves in Lead 4, and a very long QT interval.

The patient was continued on thyroid and was also given ammonium chloride and vitamin B complex. He was kept on a low-calorie diet.

When discharged a month after admission, he had lost 28 pounds in weight and had become free of edema and dyspnea. Following discharge from the other hospital, he remained at home, out of bed, taking thyroid and vitamin B complex. He gradually became orthopneic at night, and began to cough frequently, bringing up fairly large amounts of frothy sputum. Six months after the onset of his illness, and five weeks after discharge from the other hospital, the patient entered this hospital.

An older sister had been studied previously at the same hospital because of the strikingly similar complaints of unexplained dyspnea and edema of the ankles, face and abdomen. Her heart was much enlarged, and in complete block, as shown by the electrocardiogram. The basal metabolic rate was –4 per cent. She was twice tapped for ascites. Death occurred about a year after onset of her illness. At the time the patient entered this hospital, a younger brother was just beginning to complain of dyspnea. He had been gaining weight. Some years previously, a physician found that he had a "large liver," during the course of an appendectomy.

On examination, the patient appeared normally developed and somewhat obese. He was orthopneic, but was not acutely ill. His complexion was ruddy. There was moderate edema of the eyelids, sacral soft tissue and both ankles. There was shifting dullness in both flanks. The liver did not pulsate, and its edge was smooth and was felt three fingerbreadths below the costal margin. The veins in the neck seemed slightly distended. Cardiac dullness extended into the axilla, with a diffuse apical impulse at the anterior axillary line in the fifth interspace. A soft systolic murmur was present at the mitral area. The rhythm was regular. The lungs seemed normal.

The temperature was 100.2°F., the pulse 50, and the respirations 24. The arterial blood pressure was 112 systolic, 80 diastolic. The venous pressure was equivalent to 250 mm. of water, in the right antecubital vein.

Examinations of the blood and urine were essentially the same as those at the other hospital. An electrocardiogram again showed complete block, with an auricular rate of 110 and a ventricular rate of 45. The T waves were flattened. A roentgenogram of the chest was similar to the earlier film, so far as the heart was concerned. There was also an area of increased density in the right cardiophrenic angle anteriorly, adjoining the diaphragm.

The patient became progressively more dyspneic. Three days after admission, Cheyne–Stokes breathing developed. The next day, there were several coughing spells in which the patient brought up blood-streaked sputum. He complained of pain in the left calf, and the leg was tender to palpation. The temperature varied between 99 and 102°F. On the evening of the fourth hospital day, he had a number of transient convulsive attacks in which his eyes rolled upward and respirations became rapid and gasping. Two hours later, he expired.

Differential Diagnosis

Dr. Ashton Graybiel: The medical history in this case begins with the appearance of symptoms without obvious cause; there is no story of any antecedent illness. Weakness and dyspnea, the first symptoms, were soon followed by massive edema. At that stage of the illness, kidney disease, as well as heart disease, was probably considered. Chronic nephrosis seems to be ruled out by the small amount of albumin found in the urine and the normal albumin-globulin ratio. Similarly, a nephrotic type of glomerulonephritis appears to be unlikely because of the relatively unimportant urinary findings and the normal blood pressure, nonprotein nitrogen and kidney function. Amyloid disease may involve the heart as well as the kidneys and other organs, and heart failure as a result of amyloid disease has been described. However, there is no known background for the development of amyloid disease, and the blood and urinary findings do not suggest amyloid nephrosis.

The electrocardiographic findings are of more than passing interest; it would be helpful to know whether there was any abnormal axis deviation.

Dr. Paul D. White: The abnormality consisted of bundle-branch block, with left-axis deviation and low voltage of the QRS waves.

Dr. Graybiel: In the presence of bundle-branch block, axis deviation cannot safely be relied on for the determination of ventricular preponderance. The very long QT interval deserves comment. It may be quite long in heart block — as long as 0.5 second. It is abnormally long in hypocalcemia, in certain types of severe heart disease with marked dilatation of the heart, and in other pathologic states. Complete auriculoventricular block in any type of heart disease is relatively uncommon: a few years ago, we had observed only 72 cases in this hospital. It is of interest that 4 of these 72 were undoubtedly of congenital origin, and this was the likely etiology in 2 others (over 8 per cent). One of the 6 cases of complete heart block of congenital origin was in an infant whose twin brother had high-grade heart block with a slow ventricular rate. In the case under discussion, the possibility of congenital heart block must be strongly considered; it is very unusual to have complete auriculoventricular block in two young

siblings on the basis of any type of heart disease other than congenital.

May we see the x-ray films?

DR. JAMES R. LINGLEY: We do not have the previous x-ray films for comparison. These films show gross enlargement of the heart, the enlargement being general but most marked in the region of the left ventricle. There is also distinct prominence in the region of the left auricle. This shadow in the right cardiophrenic angle interests me very much because we have seen right-sided diaphragmatic hernias that looked like that. There may be herniation of the transverse colon through the right side of the diaphragm, or a herniation of the omentum. A barium enema was advised, but evidently the patient was too ill to have that examination. It could have been a pericardial cyst or a localized encapsulation of fluid, but both possibilities are unlikely.

DR. GRAYBIEL: Do you think that there was pericardial effusion?

DR. LINGLEY: I do not believe that there was any pericardial fluid.

DR. GRAYBIEL: The coughing spells shortly before death — which raised blood-streaked sputum and were associated with pain and tenderness in the calf — raise the question of pulmonary emboli. It is even conceivable that the illness began with an embolus that lodged in the pulmonary artery and caused preponderant right-sided heart strain and congestive failure; such cases have been described.

Finally, the terminal event may have been due to the breaking away of a mural thrombus from the left ventricle, with embolism to the brain, or death may have resulted simply from the severe degree of congestive failure.

We have, then, the unusual story of a young man who, within six months, developed heart failure and died. This story becomes the more remarkable when it is learned that a sister died of a similar illness and that both had complete auriculoventricular block. The degree and extent of the edema suggests either a severe grade of predominantly right-sided heart failure or some mechanical obstruction on this side.

It seems to me that a diffuse myocardial process must be considered as the possible cause of the signs and symptoms described. A number of cases of myocarditis of essentially unknown origin have been observed. "Isolated myocarditis" and "interstitial myocarditis" are terms sometimes used.

There is no good evidence that the heart disease was of rheumatic origin: there was no fever or joint pains, and murmurs were not heard until the terminal stages. Fiedler's myocarditis might be mentioned, but fever is a characteristic of this disease. Syphilitic myocarditis is unlikely, not only because of its rarity but because the blood Wassermann reaction was negative. An endocrine hepatocardiac syndrome characterized by cirrhosis of the liver, pigmentation and infantile regression and followed by severe heart failure has been described. However, most of the characteristics of this syndrome were not present. Von Gierke's (glycogen-storage) disease must be mentioned. But this diagnosis seems unlikely when it is recalled that the patient was able to work as a truck driver until six months before admission to the hospital. Pericarditis with effusion is a possibility, and even the appearance of the heart in the x-ray film is not inconsistent with a considerable amount of fluid in the pericardium.

Nevertheless, I am led back to the original idea that in this case there was a myocarditis of essentially unknown origin that produced an extreme degree of cardiac enlargement, and that there may have been a mural thrombus, a portion of which broke away to cause cerebral embolism and death.

DR. WHITE: I came in contact with this case, having had correspondence with the patient's physician in another city, who spoke about the mystery of the illness and asked if we could take the patient for study. Although he lived only four days after arrival, we were able to make a satisfactory study; and he had been in the other hospital long enough to have even more complete studies.

Dr. Frank N. Wilson, of Ann Arbor, Michigan, was asked for an opinion. He wrote:

> The story that you give in your letter is very peculiar and interesting. Complete heart block in young people is unusual. It is seen in congenital heart disease occasionally but almost always, if not always, in association with a defect in the ventricular septum and consequently with a systolic murmur that is loudest in the central part of the precordium. I have recently seen one case in which heart block may possibly have been due to myxedema, and it might be worth while to try the effect of desiccated thyroid. Syphilis of the myocardium, without definite evidence of involvement of the aorta, is extremely uncommon but does occur. It would be extremely unlikely in a man of twenty-one. Vitamin B_1 deficiency is said to cause very striking changes in the heart at times, but I do not believe that heart block has been reported. A severe deficiency of this type, with edema, is common, but there are neurologic changes. I take it that there is nothing in the history to suggest a deficiency disease. Marked enlargement of the heart may occur in sickle-cell anemia, which of course is, practically speaking, confined to Negroes, and in pituitary disease, particularly acromegaly. There does not seem to be any suggestion of this last condition here.

There is also a letter from Dr. Robert S. Starr, of Hartford, Connecticut, who had seen the patient. His final opinion was as follows:

It is doubtful whether congenital heart disease of any type could have been present throughout this boy's life without causing some degree of incapacity previous to the present illness. Moreover, the absence of murmurs and other objective evidence of congenital heart disease makes this diagnosis unlikely. Electrocardiograms, however, seem to indicate that the interventricular septum is rather particularly involved in the disease. The remarkable size of the heart by x-ray examination and the somewhat definite left ventricular and left auricular enlargement are noteworthy, but the symptoms so far have been chiefly those of failure of the right heart. Von Gierke's disease, although it must be considered, seems doubtful in the absence of a large liver.

I can add nothing except the note that I made on the ward the second day after admission:

Marked cardiac enlargement — dilatation and hypertrophy — with failure, and extensive involvement of the auriculoventricular conduction system (complete heart block and left bundle-branch block). A very bizarre syndrome at this age, not fitting in with any ordinary cardiac diagnosis (rheumatic, congenital, coronary or diphtheritic). It is possible, from the family history, x-ray findings and absence of other etiology, that rare neoplastic disease or von Gierke's (glycogen-storage) disease may be responsible. It is not likely that we shall be able to establish an ante-mortem (or perhaps even a post-mortem) diagnosis.

Clinical Diagnoses

Congestive heart failure.
Von Gierke's disease.

Dr. Graybiel's Diagnoses

Myocarditis, of unknown origin.
Complete auriculoventricular block, ? congenital origin.
Cardiac enlargement, marked.
Congestive failure, marked.
Mural thrombi and cerebral embolism?
Pericarditis, with effusion?
Pulmonary embolism?

Anatomical Diagnoses

Idiopathic hypertrophy and dilatation of the heart.
Mural thrombus, right auricle.
Pulmonary infarcts, multiple.
Anasarca.
Chronic passive congestion.
Thrombosis of posterior tibial veins.

Pathological Discussion

Dr. Tracy B. Mallory: Dr. White's last statement is perfectly true. This man had an enormously dilated, moderately hypertrophied heart, one of the largest hearts from the point of view of capacity that we have ever seen, and all the chambers shared in the dilatation and in some degree of hypertrophy. The actual weight was 600 gm. The tricuspid valve measured 17 cm. in circumference, the mitral between 13 and 14 cm. They are the two largest valve rings we have ever seen. The aortic and pulmonary valve rings, however, were quite normal. The coronary arteries were entirely normal. We made many microscopic sections of different areas of the myocardium, and none of them showed abnormality. The muscle fibers were somewhat larger than normal, but they showed no vacuoles of either glycogen or fat. There was not the slightest trace of inflammatory reaction to suggest myocarditis. The epicardium showed numerous petechial hemorrhages, which were found in various other spots in the body. It was noted that the blood had not clotted post mortem. Such failure of post-mortem clotting is suggestive evidence of an asphyxial death. There was a thrombus in the left auricular appendage, which could have been the source of five pulmonary infarcts that were found. On the other hand, the patient also had thrombosis of both posterior tibial veins, and I think that is the more probable source. Although there were several emboli, they had not produced large areas of infarction, and none of them were of sufficient size so that one could attribute death to pulmonary embolism. We made glycogen stains of various other organs, as well as of the heart, to be perfectly sure that we were not dealing with von Gierke's disease, and no abnormal deposits were found. The kidneys showed nothing that could not be explained by passive congestion.

Dr. Donald S. King: How about the shadow on the right side of the heart?

Dr. Mallory: Perhaps that was one of the pulmonary infarcts.

Dr. White: Each year, at the time of our graduate courses, we try to present one such case as this. It is not only very humbling, but it is also stimulating for our own further studies.

Dr. Mallory: A year ago, an almost identical case[1] was presented, an older man, forty years of age, with marked hypertrophy and dilatation of the heart and absolutely nothing to explain the condition. Such cases have been reported in small numbers. Levy and Rousselot[2] reported 3 cases clinically similar, but 2 of these cases showed degenerative changes in the ventricular muscle.

A Physician: There was no pulmonary endarteritis?

Dr. Mallory: No.

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1. Case records of the Massachusetts General Hospital (Case 26401). *New Eng. J. Med.* 223:547-550, 1940.
2. Levy, R. L., and Rousselot, L. M. Cardiac hypertrophy of unknown etiology in young adults: a clinical and pathological study of three cases. *Am. Heart J.* 9:178-195, 1933.

The New England Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established in 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society

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Subscription Terms: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.04 per year, Boston funds; $8.52 per year for all foreign countries belonging to the Postal Union.

Material for early publication should be received not later than noon on Friday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

PROCUREMENT AND ASSIGNMENT SERVICE

An urgent call to all physicians to enter military service in the present emergency appeared in the January 1 issue of the *Journal*, as well as in the December 27 and January 3 issues of the *Journal of the American Medical Association*. The following statement by the Procurement and Assignment Service concerns the response of the medical profession and contains additional information that is of interest to those who, for one reason or another, cannot enlist in the United States Army or Navy:

The response of the physicians of the country to the Procurement and Assignment Service request for enrollment of those now ready for immediate service in the United States Army or Navy is highly gratifying. All names are being processed and those who meet the present demands of the Surgeons General will receive application forms and authority to appear for physical examination at an early date. All who are now ready for immediate duty should forward applications to the Procurement and Assignment Service at once. It is not the intention of the Procurement and Assignment Service to register every physician, dentist and veterinarian at the present time. Only those available for immediate assignments should register at this time. The physical requirements of all military, governmental, industrial, and civil agencies will be published in national and state journals immediately. On the basis of this information every physician, dentist and veterinarian will be able to make a self-appraisal of his physical qualifications. Within a few weeks the Procurement and Assignment Service will mail to all applicants a form on which they will be asked to state their preferences for assignment to all agencies of national defense which require medical, dental and veterinary personnel and for service in communities in public health and other civil categories. In this way every physician, dentist and veterinarian of the country will be able to lend maximum support to the national emergency. In order to meet the expanding needs of the military services, every physician immediately available for duty should mail his application blank to the Procurement and Assignment Service at once. All others will be given an opportunity to volunteer in the near future.

FRANK H. LAHEY, M.D., Chairman
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Executive Officer

UNITED WAR FUND CAMPAIGN

The Greater Boston United War Fund Campaign, which begins on January 22 and will continue until February 11, represents a concerted endeavor on the part of the Greater Boston Community Fund, the American Red Cross, the United Service Organizations and the local Soldiers and Sailors Committee to raise $7,600,000—nearly $3,000,000 more than the goal of the Community

Fund last year. Boston is the only community of comparable size in which such a joint campaign is being conducted. Success therefore becomes a matter of civic pride and an example to other cities.

The campaign epitomizes the war effort of the Nation — the answer of free men to the threats of slaves and tyrants. For the money contributed, which will eventually have the effect of supporting the men in battle, is given voluntarily by those who wish to affirm their belief in the worth of liberty and justice. The American Red Cross sustains the morale of the armed forces in the field, distant outposts and hospitals by providing a link of communication between these men and their families; in addition, it must provide shelter, food, clothing and medical aid to the civilian victims of bombing, sabotage and other disasters. The United Service Organizations and the Soldiers and Sailors Committee direct their activities toward maintaining the morale of the service men. The Community Fund guards the vital home front: it protects the general population against poverty, sickness and despair — a trilogy that is potentially more menacing than armed invasion.

The war is on. Already, Pearl Harbor and Manila have become names to be remembered, names that mean temporary and honorable retreat before a treacherous, and therefore unexpected, assault. If the men who gave their lives in those battles are to be vindicated, every effort against the enemy must be supported. And the United War Fund Campaign represents such an effort.

The enormous goal can be attained only through the generosity of those who contribute. And this means sacrifice at a time when the burden of unprecedented taxation is becoming a reality. The quota of the Physicians' Group, $37,415, is an increase of nearly 100 per cent over the total raised in last year's campaign. Physicians, accordingly, may well wonder how they can be expected to give such a sum: the number who are able to give contributions of several hundred dollars is decreasing; the doctor, like everyone else, faces a discouraging rise in his tax rate; and many medical officers have already begun duty with the Army and Navy. The only solution is for *all* physicians to give. Those who have given before must be even more generous, and those who have not supported previous campaigns must contribute in proportion to what they have.

The United War Fund Campaign should be considered a call to arms for those who are being protected, after all, from the full shock of enemy attack. Moreover, the campaign is a challenge to all who prize their liberty sufficiently to fight for it. It is to be expected that physicians will be among the first to meet such a challenge.

MEDICAL EPONYM

Malpighian Corpuscles

"De internis glandulis renalibus, earum continuatione cum vasis [The Internal Glands of the Kidneys and Their Connection with the Blood Vessels]" is the title of the section of the discussion of the kidneys in which Marcello Malpighi (1628–1694), primarius in the Academy of Medicine at Messina, describes these structures. The quotation is taken from the edition of his *De viscerum structura exercitatio anatomica* [*Anatomical Essay on the Structure of the Viscera*], published at London in 1669, the first edition having been published at Bonn in 1666. A portion of the translation follows:

> Since we have shown in a previous section that glands are found in the kidneys, and since, as will be shown below, these perform a special function in the excretion of the urine, it is advisable to spend a little time on them. They are located in the outermost part of the kidneys, are almost infinite in number, and probably correspond to the urinary vessels, which join to make up the main bulk of the kidneys. They are gathered into separate bundles, more than forty in number, and it is by virtue of these that those small divisions arise which appear in all kidneys. Wherefore, no definite description of their shape can be given on account of their minuteness and transparency, which is their chief characteristic: they seem, however, to be round like fish eggs, and while a black humor is passing through the arteries, they turn black; one might say that all round them they have shoots, moving like twining tendrils, so that they appear to be wreathed around, so to speak — with this exception, however, that the main part, which is fastened to the branch of the artery, turns black, whereas the rest retains its own color.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Analysis of Causes of Maternal Death in Massachusetts During 1940 (*continued*)

Embolism

The immediate cause of death in 28 cases was embolism. Table 1 presents an analysis of these cases.

After normal delivery. A cerebral embolus occurred in 1 patient who was suffering from pulmonary tuberculosis. It was stated that she had only a short time to live in any event, and that the pregnancy had simply shortened her life. Three patients died after they had left the hospital—2 within twenty-four hours and 1 ten days later. It

Table 1. *Deaths due to Embolism.*

Occurrence of Embolus	No. of Deaths
After normal delivery	11
After operative delivery	7
After cesarean section	5
After abortion	2
During pernicious vomiting	1
During labor	1
After a separated placenta	1

is interesting that no serious pelvic operation preceded these embolic deaths. In 1 case, the patient delivered herself at about seven months; a few days after delivery, she was operated on for acute appendicitis and intestinal obstruction, and subsequently for a postoperative abscess. This patient died very suddenly just as she was leaving for home. The pregnancy may have obscured the diagnosis of appendicitis, because it was not definitely recognized until after delivery, although there had been symptoms preceding labor; this was a surgical death, but the immediate cause was embolism.

After operative delivery. In the 7 operative cases, 1 patient was delivered by version. She ran a febrile convalescence, and it is quite likely that an incomplete rupture of the uterus was sustained at the time of the delivery. One death occurred abruptly seven hours after delivery, and was undoubtedly due to embolism. One patient who was delivered by a low-forceps operation died the day after she arrived home; it was said that her convalescence had been entirely normal while she was in the hospital. Another patient developed an embolus three days after leaving the hospital and died abruptly. Another died on the ninth day, when she got out of bed. In 1 case, in which a low-forceps delivery was performed, the patient had an embolus about twenty minutes after delivery, and died four hours afterward. One patient, who developed respiratory embarrassment at the beginning of anesthesia, never recovered. Of course, it cannot be ruled out that the anesthetic was not the cause of this death, but the history suggests embolism. One patient delivered by low forceps developed respiratory embarrassment after 9 gr. of Nembutal and 1/150 gr. of scopolamine. The cyanosis was associated with much mucus and no vomiting; no anesthetic was given. This death was ascribed to embolism, although barbiturates may have really been responsible. The doses in this particular case were 3 gr. of Nembutal at 2:00 a.m. and 4 gr. at 6:00 a.m., with 1/150 gr. of scopolamine. About the only medical criticism in the treatment of these cases is that in the patients who left the hospital and died a few days after reaching home, phlebitis probably existed in each case and had not been diagnosed.

After cesarean section. There were 5 fatal cases of undoubted pulmonary embolism following cesarean section: 1 on the sixth day; 1 on the tenth day; 1 on the fifth day; 1 in a patient who was about to leave the hospital; and 1 four weeks following the operation as the patient was about to be discharged. The last patient had had an initial embolus at ten days. The number of deaths from embolism after cesarean section emphasizes the fact that fatal emboli are much commoner in cesarean sections than in normal deliveries. Embolism has always been recognized as a hazard of abdominal surgery, and because of this hazard, cesarean sections should never be entertained lightly.

After abortion. Miscarriage occurred in a patient one day after she had been operated on for acute appendicitis. Apparently, she was convalescing normally when suddenly, nine days later, she went into a state of shock and died. One case of self-induced abortion was definitely septic. After she reached the hospital, this patient had been treated in the most approved manner—with transfusion, blood culture, no interference with the uterus and sulfanilamide therapy. Undoubtedly, the embolus that caused her sudden death came from a thrombus in the pelvic veins. This case was turned over to a medical examiner, but no autopsy was performed.

During pernicious vomiting. In the case of pernicious vomiting, the patient died without operative interference. No attempt was made to interrupt the pregnancy, and it is probable that intravenous therapy had something to do with this death because the distress began three hours after intravenous glucose medication, and death occurred three minutes later. But, since this woman

was pregnant, the death was classified as a maternal death.

During labor. In a case of abnormal presentation, the patient died during labor. She was treated conservatively until full dilatation, and while being prepared for anesthesia, developed a severe pain in the chest and died within two minutes. In no way can the handling of this case be criticized. Unfortunately, an autopsy was not performed.

After a separated placenta. In the case of separated placenta, the patient was treated conservatively by cervical packing and an abdominal binder; although she had an anuria, which cleared up so that she passed 1200 cc. of urine on the ninth day, that evening she developed acute pain, cough and bloody sputum, and died eight hours later. One does not know how to prevent such a catastrophe.

* * *

On the whole, a review of these deaths from embolism shows that most of them, in the present state of knowledge, are unavoidable. Patients who had been running slight fevers and died as they were about to leave the hospital, or a few days after they had returned to their homes, were not treated so conservatively as present knowledge teaches. It is possible that some of these cases might have been prevented had a diagnosis of phlebitis been made and had the vein at fault been operated on. This is a new branch of surgery, and at present only those who have had large experience in vein surgery should pass on each individual case. It has been suggested that heparin be used on operative deliveries when the element of trauma has been excessive. Since most of the cases of embolism were not associated with operative procedures, it seems as though the incidence following such procedure was not so great as it had been thought, and the cost of heparin therapy is still so prohibitive that any extensive research in the prevention of phlebitis and subsequent embolism by its use is out of the question.

DEATHS

BYRNES — JOHN P. BYRNES, M.D., of Springfield, died recently. He was in his fifty-first year.

Dr. Byrnes received his degree from Albany Medical College in 1914. He was a former member of the Massachusetts Medical Society.

HERSAM — NORMAN P. HERSAM, M.D., of Stoneham, died January 15. He was in his fifty-eighth year.

Dr. Hersam received his degree from Harvard Medical School in 1912. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow survives him.

WAR ACTIVITIES

EVACUATION SYSTEM MANUAL NO. 2

MEDICAL ORGANIZATION FOR PLAN A — EMERGENCY DISASTER

THIS IS THE SECOND MANUAL TO BE PUBLISHED RELATING TO CIVILIAN EVACUATION. ITS PURPOSE IS TO AID LOCAL SAFETY COMMITTEES IN ESTABLISHING ADEQUATE MEDICAL SERVICES IN CONNECTION WITH EVACUATION.

THE EVENT WHICH WILL MAKE AN EVACUATION OF THE CIVILIAN POPULATION NECESSARY WILL BE AN EVENT OF VIOLENCE. ITS INEVITABLE EFFECT UPON THE HUMAN BEINGS INVOLVED WILL BE THE DISRUPTION OF THEIR NORMAL CONDITION, BOTH PHYSICALLY AND MENTALLY: THE SHOCK, THE GRIEF, THE LOSS AND THE EXPOSURE WILL CREATE MANY MEDICAL PROBLEMS. THESE PROBLEMS MUST BE MET EFFICIENTLY AND PROMPTLY NOT ONLY FOR HUMANITARIAN REASONS BUT ALSO FOR REDUCING TO THE MINIMUM THE LOSS WHICH THE ENEMY SEEKS TO INFLICT.

J. H. SHERBURNE, *Director*
Evacuation Division
Massachusetts Committee on Public Safety

Two previous publications dealing with civil evacuation have been issued by the Massachusetts Committee on Public Safety. *Bulletin No. 1: Evacuation of Civilians* considered the problem inherent in evacuation and gave information to be used in making evacuation plans. *Manual of Evacuation System, No. 1: Organization Plan A — Emergency Disaster* defined plans of evacuation to meet different types of emergency, described the organization to be developed and discussed the operation of these plans. The present manual is intended to describe the medical aspects of evacuation and the duties of evacuation medical officers. All evacuation medical officers should be thoroughly conversant with the previous publications.

Bulletin No. 1: Evacuation of Civilians was concerned with the removal of certain priority groups from danger zones to places of relative safety. Since its publication in June, 1941, the duties of the Evacuation Division have been broadened to include the evacuation and emergency care of all groups, except casualties, in the civilian population in the event of bombing or other war disasters. Obviously this is disaster relief, which is one of the major activities of the American Red Cross. It is therefore of the utmost importance that there exist the greatest cooperation between officers of the Medical Division, the Evacuation Division and the Red Cross, in order that there may be full utilization of all available resources. Red Cross facilities are to be augmented, not supplanted. It has been agreed between the Red Cross and the Evacuation Division that the former will supply, in so far as possible, ambulance service, mobile canteens, food, clothing, bedding, supplies and temporary shelter. Nursing care may also be provided, principally in the form of nurses aides. Medical personnel is furnished by the Evacuation Division.

Manual of Evacuation System, No. 1: Organization Plan A — Emergency Disaster defines five different types of evacuation. Plan A, the first to be worked out in detail, provides for the care and resettlement of civilians following an emergency disaster. Plans B, C, D and E probably

would be less hurried in their execution and would provide for resettlement on a long-term basis.

Civil evacuation will be voluntary except when compulsory evacuation is executed at the order of the military authorities or the government. The expense of evacuation will be met from public funds, but individuals cared for away from home will be expected to reimburse the government whenever possible for the cost of such care, either in whole or in part.

The specific objects of this Manual are as follows: to describe the duties of evacuation medical officers in the execution of Plan A; to describe the equipment and personnel needed; and to describe the various registration and examination forms and to discuss their use. Other manuals will be issued later in relation to Plans B, C, D and E.

Organization and Duties of Evacuation Medical Personnel

The organization of the Evacuation Division was described in *Manual of Evacuation System, No. 1: Organization Plan A — Emergency Disaster.* Its director will be assisted by a group of staff officers, among whom will be the chief evacuation medical officer and his deputy. It will be their duty to simplify, standardize and integrate all the medical activities of the Evacuation Division. They will be responsible for determining policies, outlining general plans and allocating evacuation medical facilities within the Commonwealth. They will send information to the regional evacuation medical officers and, through them, to the local communities. They will also maintain contact with the other divisions of the Committee on Public Safety, with the Red Cross, and with the Office of Civilian Defense for co-operative action between the states. They will have such advisory and liaison officers as are necessary.

Working under the state officers will be nine regional evacuation medical officers and their deputies. These officers will be called to duty at their regional headquarters in the event of an emergency. They will assist in every way the work of local evacuation medical officers. They should participate in the development of local evacuation facilities and arouse public interest in the work of the Evacuation Division. They control, through their district officers, all communications dealing with the medical aspects of evacuation between cities and towns in their regions. Communities needing additional medical assistance for evacuation should communicate with the regional evacuation medical officer and not with officers in adjoining localities. These might be equally affected by the disaster.

For each local evacuation officer, there will be appointed an evacuation medical officer and deputy, who will supervise the physicians, nurses and other personnel in their city or town who are working under the Evacuation Division.

An evacuation medical officer will be assigned to each report(control)-center area. He is the chief evacuation medical officer for that area, although there may be other evacuation medical officers working with him. One report center is usually organized for each 50,000 people in the State. It is the focal point from which all emergency service is rendered, and is controlled by the chief air-raid warden. Every evacuation medical officer should be thoroughly familiar with *Medical Handbook No. 2*, and also with the A.R.P. System. He should acquaint himself with all local facilities, especially those of the Red Cross, and should understand their organization. He should show the utmost co-operation in the use of these facilities. He should know that supplies and equipment exist in fact as well as on paper. Personnel should be listed by address and telephone number, and should be fully acquainted with their duties. When the Red Cross or other agencies are not able to furnish nursing personnel, it shall be his responsibility to obtain nurses from other sources.

1. Assembly Stations

Assembly stations will be selected in each community, their number and location depending on local conditions. They may be situated in buildings taken over for medical depots or may be identical in location with the casualty stations of the Medical Division. These assembly stations are under the direction of the Evacuation Division. The evacuation officer at the station will need the services of a physician, who will be provided by the Medical Division from their personnel present at the medical depot. He will be assigned to this duty by the chief medical officer at the report center. The medical officers of the Evacuation Division will not as a rule be called to duty until the temporary shelters have been selected. The chief evacuation medical officer should be sure that this arrangement is clearly understood.

It shall be the duty of the medical officer at an assembly station to reassure and calm any excited, worried or hysterical individuals — morale is of major importance and a competent individual can do much to keep it high — and to inspect all evacuees and treat any minor injuries or medical conditions that may be found.

In Appendix A will be found a list of the equipment needed at an assembly station. Arrangements have been made with the Medical Division to supply this kit and keep it filled. The chief evacuation medical officer is responsible for seeing that this equipment is kept at the medical depot and that supplies are replenished as necessary.

Any group of evacuees may include individuals subject to heart attacks, epileptic seizures and other medical emergencies, such as labor induced by the excitement of the occasion. To avoid confusion and therapeutic mistakes, each person receiving medical treatment will have this noted on an identification tag (the one used by the Medical Division), which should be attached to his person. In addition, a record must be kept of all medical treatment in a book provided for each unit. This must be returned daily to the chief medical officer at the report center at the end of each tour of duty.

2. Transport

The medical officer at the assembly station will usually have no duties in connection with the transport of evacuees to temporary shelters, unless an urgent medical situation arises. The distances to temporary shelters will be short.

3. Temporary Shelters

The medical officers of the Evacuation Division are responsible for medical care at the temporary shelters. As soon as the location of a temporary shelter has been selected, the chief evacuation officer will notify the chief evacuation medical officer who should at once go to the medical depot, collect his equipment and proceed to the temporary shelter. This chief evacuation medical officer will also call to duty sufficient nursing personnel. He will be responsible for the medical care of evacuees until the temporary shelter is cleared. Provision must be made for relief personnel, if necessary.

At the temporary shelter, considerable medical care

may be needed. The required equipment (Appendix B) will be supplied by the Medical Division. The chief evacuation medical officer is responsible for seeing that this equipment is on hand and kept in an appropriately labeled container at the medical depot. The evacuation medical officer will be responsible for having this kit brought to the temporary shelter when he goes on duty.

The medical personnel supplied to a shelter will vary according to the number of evacuees. There should, if possible, be at least one nurse for every one hundred evacuees, and aides should be supplied in the same ratio. Volunteers may be used for clerical help. All the facilities of the Red Cross will be needed, and should be used to the fullest extent.

All medical treatment must be recorded. If an identification tag was attached to the evacuee at the assembly station, the treatment should be noted on this tag, or if the evacuee is untagged, a tag should be attached and the entry should be made thereon. If, however, the evacuee has been registered, the entry can be made directly on the evacuation registration card (see below). All identification tags should eventually be removed and filed, and any entries made thereon should be copied on the evacuation registration card. A record of treatment must also be kept in the book provided with the medical kit.

Registration of evacuees by card will be done for administrative purposes and does not directly concern the medical officer. However, inasmuch as some persons will require emergency treatment, and since, under certain conditions, mass immunization may be necessary, space will be provided on these evacuation registration cards for medical information.

The chief evacuation medical officer or his deputy should be available to advise and consult with evacuation officers at information centers (see *Manual of Evacuation System, No. 1*) in the disposition of evacuees with medical or medicosocial problems. He should have a thorough knowledge of the Evacuation System, and should be conversant with the medical difficulties likely to be encountered in caring for children and persons handicapped by age or illness.

4. Resettlement

Most of the evacuees will find permanent quarters for themselves and will need no medical examination other than the cursory inspection given at the assembly stations and temporary shelters. Those who have received some medical treatment should be given instructions concerning continuation of medical supervision, if necessary. There should be consultation with the Medical Division regarding facilities. A small percentage of the evacuees will require billeting by the Evacuation Division. These persons will have a medical registration card and will receive a medical examination. So far as possible, evacuees will be housed in the locality, but they may be moved into another community, another region or, in the event of a major disaster, into another state. The chief evacuation medical officer in the place receiving them, wherever it may be, will act in accordance with procedures for a reception area, which will be considered in another manual.

For the medical registration of evacuees, cards of varying colors will be used, to permit rapid sorting by priority groups. The system will be as follows:

White — Healthy persons over fifteen years of age.

Blue — Healthy children, five to fifteen years of age.

Green — Healthy children under five years of age.

Red — Expectant mothers.

Orange — Cripples, the aged and infirm, and handicapped individuals regardless of age.

The term "healthy" is to be liberally interpreted. It should include individuals having slight handicaps, such as mild cardiac disease, malnutrition and other defects not limiting normal activities to any significant degree.

Such a system of classification will expedite the sorting of evacuees and aid in determining to what extent special medical facilities will be required. For example, plans will have to be made for the care of the aged in special homes, for the delivery of pregnant women in maternity hospitals and for the care and treatment of persons with such handicaps as blindness, crippling, mental deficiency and convulsive disorders.

Medical examination. The medical registration card, which will go with the evacuee to the area in which he is resettled, should include a record of medical examination, which will be the beginning of a cumulative medical record.

Detailed and inclusive physical examinations do not seem necessary or feasible in view of the complexities and confusion of any evacuation and the possible shortage of medical personnel. The examination should be considered a rough screening process designed to eliminate individuals with contagious disease or serious handicaps. In children, the conditions most likely to be encountered are the exanthems, impetigo, pediculosis, scabies and, in young girls, vulvovaginitis. Adults should be inspected for the exanthems, even though the probability of their contracting them would not be great. Examination for tuberculosis, syphilis and gonorrhea does not seem practical under these conditions.

Part of the medical inspection can be done by a nurse, leaving the physician to devote his time to the more important phases of the examination (about five minutes should be allowed) and to make final judgment in doubtful cases. Individuals over fifteen years of age should have a brief examination of the lungs and heart. Volunteer workers may be used for clerical assistance.

Evacuees who show signs of acute illness sufficient to make bed care necessary or who have developed any of the exanthems must be hospitalized. Arrangements for hospital and isolation facilities will require the co-operation of the Medical Division. If serious conditions are encountered, individuals should be sent by ambulance to the nearest hospital. Minor contagious conditions, such as impetigo, scabies and pediculosis, should not prevent the transportation of affected evacuees. If such individuals are to travel long distances in large groups, they should be segregated during their travels, and treatment should be begun as soon as they reach the reception area. In addition to the medical registration card, which will go with the evacuee to his final destination and there be kept in the custody of the chief evacuation medical officer, a travel tag, indicating the evacuee's medical status, will be provided. This will facilitate the handling of mildly contagious evacuees. It will be attached to his person after he has undergone his medical examination.

Transportation. The transportation of evacuees will not be difficult when they are resettled locally. Except for the sick and the handicapped or for those in large urban centers, many of them will be able to walk to their destination. However, evacuees may have to be moved in large groups and for a considerable distance, in which case more detailed plans will be necessary. Under these circumstances, as soon as evacuees have been registered and have passed the medical examination, they will be grouped and assigned to whatever buses, automobiles or trains may have been reserved for them. The evacuation officer in charge of each party shall be responsible for the

medical registration cards during transport, and shall deliver them to the chief evacuation medical officer at the resettlement area.

Healthy adult refugees will not need any more supervision in transit than would be provided by the transport officer in charge of the party, except when they travel in large groups. Healthy children from five to fifteen years of age will be adequately supervised by their school teachers or other individuals to whom this duty is delegated. More care will be required for young children, and medical supervision will usually be reserved for them and for handicapped evacuees. Special arrangements for such groups will be made by the local evacuation officer after consultation with his evacuation medical officer, his transport officer and any other interested parties.

It is assumed that each trainload or convoy of evacuees will at least be accompanied by persons who have had adequate Red Cross training and who have first-aid supplies to deal with minor emergencies.

If evacuees are transported distances requiring a traveling time of several hours, it is to be anticipated that medical emergencies will occasionally arise. Certain towns should be designated along the route where patients may be left in the hands of the local evacuation officer. If possible, he should be warned by telephone or telegram of his approaching responsibility, so that he may have time to make arrangements before the evacuee arrives.

If evacuees travel by auto or bus, they will probably arrive at the resettlement area directly. If, however, they go by rail, intermediate steps may be necessary before final billeting. Local evacuation medical officers must therefore arrange for certain medical facilities at disembarkation points. They and their aides should have armbands, uniforms or other distinguishing insignia. Equipment such as that described for assembly stations should be on hand.

This bulletin will not deal with the medical problems to be encountered in resettlement areas. It is obvious that long-term medical care of evacuees will require special planning. There will be time for epidemics of communicable disease to occur, and some control system must be set up. It may be necessary to arrange for clinic, hospital and domiciliary care of evacuees. The mental effects of bombing, separated families and strange surroundings will create new, and often disturbing, problems, especially among children. This phase of the evacuation process will be discussed in a later manual.

APPENDIX A. *First-Aid Equipment for an Assembly Station.*

6 pkg. Bandage compress, 3 in., 2 per pkg.
2 pkg. Tannic acid jelly
2 pkg. Gauze, absorbent, 1 yd. per pkg.
2 Bandages, gauze, 3 in.
4 Bandages, cravat triangle
48 Tags, identification
1 bot. Aromatic spirits of ammonia, 120 cc.
1 bot. Morphine sulfate, sterile solution, 20 cc., with rubber-diaphragm stopper (1 cc. contains ¼ gr. morphine sulfate)
1 Syringe, Luer, 2 cc.
12 Needles, hypodermic, 24 gauge
1 bot. Alcohol, 90 per cent, 120 cc.
1 pkg. Nitroglycerin tablets, 100 per pkg.
1 pr. Scissors
1 pr. Tweezers
1 Pencil, indelible
1 Flashlight
1 box Throat sticks, 10 per box
1 Stethoscope
1 pkg. Drinking cups, paper
1 Book, record

These articles should be packed in a durable, clearly labeled container such as a haversack or suitcase.

APPENDIX B. *Medical Equipment for a Temporary Shelter.*

6 pkg. Bandage compress, 3 in., 2 per pkg.
2 pkg. Tannic acid jelly
2 pkg. Gauze, absorbent, 1 yd. per pkg.
2 Bandages, gauze, 3 in.
1 Gauze kit, Red Cross
4 Bandages, cravat triangle
1 lb. Cotton, absorbent
1 bot. Aromatic spirits of ammonia, 120 cc.
1 bot. Morphine sulfate, sterile solution, 20 cc., with rubber-diaphragm stopper (1 cc. contains ¼ gr. morphine sulfate)
1 Syringe. Leur, 2 cc.
12 Needles, hypodermic, 24 gauge
1 bot. Alcohol, 90 per cent, 180 cc.
1 pkg. Nitroglycerin tablets, 100 per pkg.
1 pkg. Pentobarbital capsules, 1½ gr., 100 per pkg.
1 tube Vaseline, sterile, 45 cc.
1 pkg. Aspirin tablets, 5 gr., 100 per pkg.
1 bot. Suprarenalin solution (1-1000), 30 cc.
1 Catheter, urethral, rubber, No. 14 Fr.
1 Stethoscope
1 Flashlight
48 Tags, identification
1 pr. Scissors
1 pr. Tweezers
1 Pencil, indelible
2 boxes Throat sticks, 10 per box
1 box Safety pins
1 pkg. Drinking cups, paper
1 Book, record

These articles should be packed in a durable, clearly labeled container such as a suitcase or wooden box.

MISCELLANY

AMERICAN TRUDEAU SOCIETY

The diagnosis of clinically significant pulmonary tuberculosis is readily reached by the average practicing physician if certain fundamental procedures are used. One of the functions of the American Trudeau Society, the medical section of the National Tuberculosis Association, is to disseminate, among the general medical public, information about advances in these procedures. The treatment of tuberculosis in general is a specialized procedure, which should at least be initiated with the counsel of a specialist. The American Trudeau Society offers a forum where practitioner and specialist can meet to discuss the technical problems involved, as well as their practical application, and the following remarks of its president, Dr. Harold G. Trimble, are of interest.

* * *

The American Trudeau Society is a natural outgrowth of the American Sanatorium Association, which was formed in the days when most of the medical problems of tuberculosis revolved around the various tuberculosis institutions and when many of the men in tuberculosis work

came by their interest because of their own personal history as tuberculosis patients. With increasing diagnostic facilities and with advances in various forms of treatment, general medical interest in diseases of the chest, including tuberculosis, was significantly increased and many young physicians became interested in these problems as such.

Theoretically, it seemed profitable, and practically it so developed, that contact between what one may call the "pure" specialist in tuberculosis and the internist, who although having other interests was intimately concerned with diseases of the chest, would benefit both. On this basis, then, with the co-operation of the National Tuberculosis Association, the American Trudeau Society was formed — an organization of medical men with a nucleus of those interested primarily in tuberculosis and including a group interested in general internal medicine.

The idea of such a society, which would be inclusive rather than exclusive, — that is, not confined to men who were primarily specialists in diseases of the chest, — caught hold among the medical public, as evidenced by the rapid increase in members. Such an organization has a dual responsibility: to push forward the already rapidly advancing knowledge of the technical medical as well as the public-health aspects of tuberculosis, and to see that the known facts are disseminated even more rapidly among physicians in general. These functions are best achieved through the work of strong active committees with as wide a geographic distribution as possible, and with a diversity of personnel to bring forth all aspects of the problem at hand. There are but few physicians of prominence in the field of tuberculosis or its closely allied specialties who are not active members of the American Trudeau Society. Members give generously of their time, talent and information to work out special problems that may be referred to them, or that they consider worthy of further investigation and study.

To provide information that is interesting, accurate and well thought through, to avoid mere novelties without overlooking new developments of intrinsic merit, and to review new phases of old problems is no mean task. This is the work of the Program Committee in arranging the annual meeting. If attendance is an index, their efforts have been crowned with success.

As new technics develop in the field of laboratory medicine in problems allied with diseases of the chest, it is essential that the procedures be independently evaluated, not by single individuals but by a group of physicians who are actively working in the same field, and who have the facilities and personnel to try out the particular method, without bias or undue enthusiasm. This is a task of the Committee on Standard Laboratory Procedures, and reports from this group are issued as promptly as possible.

Progress in the fields of diagnosis and treatment is based largely on technical developments in allied sciences. It is not always that these newer developments get to the medical student rapidly and effectively. The Committee on Undergraduate Medical Education, consisting of men who are experienced in teaching and alive to the needs of both student and medical school, is seeking more effective ways to reach this end.

The problem in postgraduate medical education is somewhat different. Practicing physicians are largely creatures of habit: they change but slowly technics that they have learned and used so long. Only when something is really better, a distinct improvement and not merely different, will it be adopted. The purpose of the Committee on Postgraduate Medical Education is to make available as rapidly as possible knowledge of diagnostic technics in the field of pulmonary disease, particularly where it should be used the most, namely, in the office of the physician in general practice. The realization that tuberculosis in its earliest stages, when it is most curable, must be actually sought — since it is ordinarily without signs or symptoms — is still somewhat of a mental hazard for men who were taught years ago that fever, cough, sputum and so forth are indicative of tuberculosis, and that proper skill with the eyes, fingers and ears is adequate for diagnosis. As many new methods of using the x-ray become simplified, more readily accessible and less expensive, the known facts regarding their effective use need to be widely disseminated. The committee is seeking to analyze the results of actual methods that have already been put into practical use and to get such information not to the tuberculosis specialist alone but particularly to the man in general practice.

New methods of x-ray procedure in the diagnosis of pulmonary conditions are in the course of rapid development. The Committee on X-ray Apparatus and Technique consists of men actively working in the application of x-rays to tuberculosis as a clinical problem, as well as those working on technical improvement in existing apparatus. This group is in a position to evaluate the developments of the x-ray and to give this information to the members and the general medical public.

The tuberculosis sanatorium is, and should be, the focus around which the tuberculosis work of all kinds revolves. As the character of treatment changes, as more technical diagnostic procedures, such as bronchoscopy, develop, and as surgical collapse therapy grows in extent, there must necessarily be some alteration in the physical plant as well as in the type of medical care available for the tuberculous patient. The Committee on Tuberculosis Sanatorium Standards is now in the midst of evaluating these problems, and will be able to report what is considered adequate current practice within the near future.

The policy of the American Trudeau Society, as originally adopted and reaffirmed on numerous occasions, has been that one seeking official certification as a specialist in tuberculosis should have a broad background in internal medicine. To that end, the Society has a committee that co-operates with the American Board of Internal Medicine.

Thousands of professional workers, such as nurses, social workers and health officers, as well as many members of the general population, have served as board members of tuberculosis associations, on seal-sale committees and in various other capacities. They have a real interest in the developments of technical problems in the field of tuberculosis. To give them authentic advice, advisory committees have been set up for the purpose of reviewing such literature of the National Tuberculosis Association as is already available, as well as checking new publications as they are produced. The Committee on Educational Literature and the Committee on Medical Information must necessarily work in very close relation with these large groups of professional and lay persons interested in the general field of tuberculosis. This work to date has been effective, stimulating and productive of much good result.

This, in outline, is the general philosophy, and its practical application, of the American Trudeau Society. Its work covers those phases of the medical aspects of tuberculosis that are mostly problems for the specialists, as well as those that have special appeal to the physician in general practice. Its effectiveness can continue only so far as both these groups bring to it their current prob-

lems and, working through its committees, bring to bear jointly the sound advice and earnest counsel that is only theirs to give. — Reprinted from *Tuberculosis Abstracts*, January, 1942.

CORRESPONDENCE

TRAUMATIC EMPHYSEMA OF THE MEDIASTINUM

To the Editor: The clinical note in your number of May 29, by Dr. Gerald L. Gaudrault and Dr. Duncan M. Chalmers on the emergency treatment of traumatic emphysema of the mediastinum had an especial use and interest when read in England, which the march of events now spreads to include America.

In peace time, this condition is but rarely observed, and as a result it more usually receives post-mortem attention than emergency treatment. With the intensive bombing of cities and with the trapping of persons under debris, it is being brought to the notice of many practitioners who are not surgical specialists. It may interest you to learn that I have seen six such cases in one evening (this, even under raid conditions, was an unprecedentedly high figure), and in all the cases the picture was complicated by an intense venous congestion. The casualties had been sitting in the basement of a building built of brick and timber, which collapsed upon them, and when contact was made with them by tunnelling some three quarters of an hour after the bomb-fall, they were buried up to about waist level in brick debris, while the remains of a light concrete ceiling sheltered their heads and shoulders. There had been considerable debris pressure over the thoracic regions. Four of the individuals were dead, and two were moribund.

The two moribund patients showed intense cyanosis and venous congestion, marked dyspnoea, pulmonary oedema, and subcutaneous emphysema in the supraclavicular region and in the sternal notch. The condition in which they were found obviously prohibited a more scientific observation, and they died within some five minutes of being found and before they could be extricated.

It is probable that the condition of the cases described above was already too advanced to be benefited by surgical intervention, but it seems obvious that medical officers must be prepared in these days to carry out the procedures outlined by Drs. Gaudrault and Chalmers. A second point, not mentioned in their paper, and which might be considered, is the benefit accruing from venesection. The relief afforded to the heart and lungs would be undoubted, and the loss of blood and any increase of shock could be compensated for by transfusion at a later and more opportune moment.

The literature on this subject does not appear to be very rich, and in peace time, it seems that most of the experience of this condition would be afforded to surgeons dealing with mine accidents — to which air-raid casualties, seen from the point of view of an urban population, approximate. It would be interesting to learn what men with mine-disaster experience have to say.

K. W. C. Sinclair-Loutit
Medical Officer for Civil Defence

Finsbury Health Centre
Pine Street
London, E. C. 1

REPORT OF MEETING

HARVARD MEDICAL SOCIETY

A regular meeting of the Harvard Medical Society was held at the Peter Bent Brigham Hospital on October 14, with Dr. James P. O'Hare presiding.

The case of a thirty-eight-year-old married woman who had entered the hospital six weeks previously because of pain in the right arm was presented. Her past history revealed no evidence of specific kidney disorder or scarlet fever. She was known to have had a negative urinalysis in 1922 while at a sanatorium for bronchiectasis. In 1927, during the seventh month of her first pregnancy, she began to show evidence of toxemia, which persisted until term. At that time, the urine showed a ++++ test for albumin and some erythrocytes, but there was no hypertension. In 1929, during a second pregnancy, she showed a trace of albumin at the fourth month and a phenolsulfonphthalein excretion of 45 per cent at the sixth month, and was delivered normally at term. There were similar findings of marked albuminuria without hypertension during two subsequent pregnancies, but apparent good health from 1935 to 1940. In 1940, the patient was found to have severe hypertension for the first time. During the previous year, there had been increasing fatigue and drowsiness, with frontal headaches, for six months, amenorrhea for five months, increased pigmentation and cramps in the extremities for three or four months and almost daily vomiting for two months. Physical examination revealed a dry, pigmented skin, exophthalmos, fundal hemorrhages without exudate, a normal heart, a blood pressure of 215 systolic, 130 diastolic, a nonprotein nitrogen of 121 mg. per 100 cc., marked albuminuria, and many erythrocytes and granular casts in the urinary sediment. On the tenth hospital day, the patient was given 500 cc. of compatible blood, with subsequent gross hematuria and a later increase in cellular casts in the sediment. Her course was one of increasing drowsiness, decreased vision, increased vomiting and an ever-increasing nonprotein nitrogen.

The case was discussed by Dr. Lewis Dexter, the speaker of the evening, who believed that this course of long-continued albuminuria, probably originating in the first pregnancy, with no previous renal history, is neither common nor rare in a patient with cardiovascular renal disease. Post-toxemic albuminuria or hypertension seems to be dependent more on the duration of this abnormality during pregnancy than on its severity, and any patient is prone to run fundamentally an albuminuric or hypertensive course until late in the disease. What causes the rather abrupt onset of hypertension after many years of albuminuria, as in this case, is difficult to explain.

The paper of the evening, "Some Recent Advances in Experimental Renal Hypertension," by Dr. Dexter, was a concise evaluation of progress in this field in the light of his own observations. He first discussed the humoral mechanism of experimental hypertension, which for practical purposes had its introduction in the work of Goldblatt and his collaborators, who, in 1934, reported that partial constriction of the renal artery in dogs resulted in a prompt and chronic arterial hypertension. Subsequently, it was demonstrated by various investigators that some humoral substances from the ischemic kidney must be a causative factor, since the same results were achieved in denervated kidneys and even in sympathectomized dogs. At present, the groups of Houssay, Braun-Menendez, Fasciolo, Leloir and Muñoz, in Buenos Aires, and of Page,

Corcoran, Helmer and Kohlstaedt, in Indianapolis, are the foremost in attempting to elucidate this humoral mechanism. To corroborate the humoral aspect, Houssay and his co-workers grafted a kidney into the neck of an animal so that the circulating blood was the only connecting link, and demonstrated that, whereas a normal kidney only rarely caused a rise of blood pressure, an ischemic graft almost invariably did. He then analyzed the venous blood from normal and ischemic kidneys and found both a vasoconstrictor and a pressor substance in the latter. The active pressor substance was isolated and called "hypertensin," and was found to be identical chemically and pharmacologically with the pressor substance produced by the in-vitro inoculation of renin and blood globulin. Renin had been found in kidneys as early as 1898 by Tigenstedt and Bergmann. Kohlstaedt, Helmer and Page, however, demonstrated that renin alone was incapable of a pressor action unless combined with a certain plasma globulin, which has been variously named "precursor" and "renin activator." Apparently, renin is, or is similar to, a globulin of the enzyme class, and is liberated from the kidney as a result of renal ischemia. Precursor is the substrate, and the term "renin activator" seems to be a misnomer. This latter component is found only in blood, not in the bodily organs. Hypertensinase is another enzymatic globulin substance, found in practically all the bodily tissues, which acts quickly to inactivate hypertensin. The Buenos Aires conception of the humoral mechanism of experimental hypertension is as follows:

$$\text{Renin} + \text{Precursor} \rightarrow \text{Hypertensin}$$
$$\uparrow \text{ (inactivates)}$$
$$\text{Hypertensinase}$$

Page and his co-workers began their investigations with purified renin and proved its inefficacy alone. They have reached essentially the same conclusions as Houssay and his collaborators regarding the nature of the reaction between renin and blood globulin (renin activator) to form a pressor substance (angiotonin), except that they postulate the presence of a so-called "renin inhibitor" and an "angiotonin activator" whose presence has not been clearly or unequivocally demonstrated. Their theory, in summary, is:

$$\begin{array}{lcl} & & \text{Angiotonin Activator} \\ & & \downarrow \text{ (activates)} \\ \text{Renin} + \text{Renin Activator} & \rightarrow & \text{Angiotonin} \\ \uparrow \text{ (inactivates)} & & \uparrow \text{ (inactivates)} \\ \text{Renin Inhibitor} & & \text{Angiotonin Inhibitor} \end{array}$$

Both the Indiana and Buenos Aires groups have demonstrated the presence of renin in the venous blood of ischemic kidneys. It is rarely present in demonstrable amounts in that of normal kidneys.

Among experiments on the role of amines in the pathogenesis of experimental hypertension may be mentioned the work of Bing on Dopa (dihydroxyphenylalanine). He has demonstrated that this substance is converted by decarboxylase (an enzyme found in renal tissue) under anaerobic conditions to a pressor amine that is probably dihydroxytyramine. Furthermore, its injection into an ischemic kidney results in a pressor effect not found when the same procedure is carried out in a normal kidney. No claim is made for an etiologic role, the ability of the kidney to produce pressor amines may eventually be found to be related to the renin, blood globulin, hypertensin or angiotonin reactions.

Dr. Dexter then discussed the relation of experimental to human hypertension. Clinically, there have been at least temporary cures of hypertension following removal of a unilaterally diseased kidney. Dogs made experimentally hypertensive run a course very similar to that of human beings. Several laboratory experiments, such as the isolation of renin from the human kidney, the changes in various clearance tests and the characteristic hypertensive response in animals to its injection further suggest a close correlation between the experimental and the clinical disease. But the results in one cannot justifiably be translated into those of the other.

Finally, there was a discussion of certain therapeutic agents that have been proposed and tried. An antibody against renin, prepared by Wakerlin and Johnson by the repeated injection of pig renin into other animals, was reported to have controlled experimental hypertension. The work was corroborated by Prinzmetal. It is considered a promising lead. Secondly, renin extracts that have long been used therapeutically for hypertension have recently been studied intensively by Grollman, Harrison and Williams, by Page, Helmer, and Kohlstaedt and by others. These extracts cause a temporary lowering of blood pressure in hypertensive animals and man as long as therapy is continued. Whether such extracts are specific or nonspecific in effect is not clear. It is known that the injection of many foreign proteins lowers blood pressure. In the reports, it is apparent that toxic reactions are sometimes noted when these extracts are injected or administered by mouth. The mechanism by which they lower blood pressure in vivo, therefore, remains in doubt. In vitro, some of the extracts contain hypertensinase (angiotonin inhibitor) as well as renin. It is barely possible that the beneficial effects of the extracts lie in the production of Wakerlin and Johnson's antibodies to renin. Much more work must therefore be done to clarify the mechanism by which renal extracts lower blood pressure.

Tyrosinase, an enzyme that oxidizes phenols, has been studied by Schroeder and shown to cause a rapid fall of blood pressure in hypertensive animals and man. In vitro, there is claimed to be destruction of angiotonin. The results appear promising. Hypertensinase is still obtainable only in crude form but is efficacious in lowering the blood pressure of hypertensive animals.

Dr. Otto Schales discussed certain enzymatic reactions in relation to that of renin and percursor and spoke in greater detail of the work of Bing and others regarding pressor amines.

Dr. Robert W. Wilkins said that, on a recent visit to the Lilly Laboratory for Clinical Research in Indianapolis, he found Drs. Page, Corcoran, Kohlstaedt and Helmer engaged in studies on the depressor substance (angiotonin inhibitor) obtained from extracts of kidney. The administration of this substance to animals or to human beings with hypertension has often been followed by a dramatic lowering of the arterial pressure. At present, the Indianapolis workers are endeavoring to purify this substance, to eliminate toxic side reactions, as well as to determine whether or not the presence of renin has anything to do with its action. They are convinced that its effect of lowering blood pressure is not the result of antibody formation. Studies of its physiologic effects show a reversal of the action of angiotonin — that is, an increase of cardiac output (ballistocardiographic) and an increase in renal blood flow, with a decrease in the filtration fraction (Smith). Dr. Page and his co-workers are confident that this substance, when obtained in its pure state, will be helpful in lowering the arterial pressure of at least certain patients with hypertension.

Dr. F. A. Simeone reported on observations made during an attempt to obtain an animal for standardization of prospective therapeutic agents. The rapid accumulation of the responsible pressor substance was demonstrated by a hypertensive response as early as three minutes following clamping of the renal artery, with a maximum response in five minutes. The site of action was determined to be peripheral rather than cardiac by denervating the heart and carrying out adrenalectomy. That a multiplicity of substances emanating from an ischemic kidney may account for some of the variable and apparently controversial reports was suggested when some animals had lowering of the blood pressure to shock levels.

Dr. Alan Moritz suggested that, should an inhibitor or neutralizing substance be found, its role in many cases would simulate that of insulin in diabetes, for the irreversible kidney changes would require constant therapy to maintain the status quo.

In reply to a question concerning the role of desoxycorticosterone in the present conception of the etiology of hypertension, Dr. Dexter stated that this hormone is now known to be effective in the hypotension of Addison's disease. Furthermore, after adrenalectomy in dogs, there is sometimes a fall in the concentration of precursor in the plasma. The injection of several of the sex hormones has been reported to elevate the blood pressure of normal animals. The exact relation of the adrenal cortex to blood pressure is, however, far from complete.

BOOK REVIEWS

Abnormal Speech. By E. J. Boome, M.B., Ch.B., M.R.C.P., D.P.H., T.D., and D. G. Harries. 12°, cloth, 162 pp. Cleveland, Ohio: The Sherwood Press, 1939. $2.50.

The authors present in rather readable style the results of their combined experience with speech disorders. They divide such disorders into three types: the functional disorders of speech, which they consider to be due to imperfect perception of speech or control of the process of utterance in spite of normal organs of speech; the organic disorders of speech caused by malformations, diseases and so forth; and the psychogenic disorders of speech due to nervous disorders. It is difficult to ascertain what the authors mean by nervous disorders. Among the functional defects are delayed speech, lalling, lisping, cluttering and such conditions as aphasia and disorders of phonation that one would expect to find usually when organic disease is present. Among organic defects are considered deafness, palatal defects and dental irregularities. The chief nervous disturbance affecting speech is considered to be stammering. The authors also include a neurotic lisp, a lateral lisp and voluntary mutism as psychogenic disorders.

Throughout the discussion, one meets expressions that are difficult to interpret, particularly those dealing with energy and brain function, in which a tense or sluggish brain producing an unrhythmic movement is described.

Regarding therapy, the authors suggest all sense-training exercises and some motor exercises to help the functional defects. The remedy of organic defects depends on the nature of the defect. The psychogenic disorders are apparently to be helped through exercises for relaxation in which the authors place a great deal of faith. Such exercises are described in detail. Following this survey of abnormal speech, there are chapters on the mentally defective child and his speech and on the "difficult" child and his speech, and a final review of recent progress in speech therapy.

The book is written for use in England, reference being made to the various dialects of that country, and its chief value to an American reader is to serve as a means of being posted on what some workers in the field of speech disorders are doing in another country.

The 1940 Year Book of Public Health. Edited by J. C. Geiger, M.D., Dr.P.H. 12°, cloth, 560 pp., with 12 figures and 24 tables. Chicago: Year Book Publishers, 1940.

This is the usual digest of current articles dealing with public health; it is noteworthy that more and more activities are coming within the circle over which the professional public-health worker casts his eye. More than four hundred articles are abstracted, and editorial comments are frequently interpolated. This is the first time that the Year Book Publishers have printed a volume on public health. The result is admirable for those whose particular interests do not lie within the larger field of medicine or for those whose interests are concentrated into smaller fields. The public-health worker himself will probably be better served by the original sources, if he has the time to peruse them. If he has not, he, too, can get a sense of proportion from this reading method.

Foundations of Neuropsychiatry. By Stanley Cobb, M.D. Second revised and enlarged edition of the work formerly known as *A Preface to Nervous Disease.* 8°, cloth, 225 pp., with 12 illustrations and 3 tables. Baltimore: Williams and Wilkins Company, 1941. $2.50.

Because the second edition of this book is based largely on neuropathology, the author has changed the title to fit his material. In addition, he has revised much of the work and slightly enlarged the book. Parts have been rewritten, and in general, the book has been greatly improved. It now forms the best study of its type in English, and should be put in the hands of every medical student. Moreover, the volume will interest a good many thoughtful physicians and will be of particular value to specialists in neurology and psychiatry. The most important addition is the section on psychopathology, which lists the main syndromes of psychiatry. In this short chapter, the author has put a large amount of material in an abbreviated but clear manner. Seldom has the reviewer seen a second edition of a book so vastly improved. Apparently, the author has read the constructive criticisms incorporated in the reviews of the previous edition.

America Organizes Medicine. By Michael M. Davis. 8°, cloth, 335 pp. New York and London: Harper and Brothers, Publishers, 1941. $3.00.

This is a thorough and excellent presentation of the relations between a changing medical profession and a changing social order. The points of contact and conflict are discussed in a way that, in the words of the author, "will not satisfy partisans but may promote thought that will diminish partisanship." The weakness of the book is that it presents the point of view of a social worker. For example, it is stated that it is profitable for the optician to turn over a portion of the sale price of eyeglasses to the physician who sent the patient—"This practice is said to be widespread." A medical collaborator would also have mentioned the much greater evil of selling eyeglasses to people who do not need them. The author is more sensitized to the economic aspects of the situation than he is to the physiologic, but his book is nevertheless a helpful discussion.

(Notices on page x)